REPORT ON THE CONSENSUS WORKSHOP ON FORMALDEHYDE

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Report on the Consensus Workshop on Formaldehyde*

The Consensus Workshop on Formaldehyde consisted of bringing together scientists from academia, government, industry and public interest groups to address some important toxicological questions concerning the health effects of formaldehyde. The participants in the workshop, the Executive Panel which coordinated the meeting, and the questions posed, all were chosen through a broadly based nomination process in order to achieve as comprehensive a consensus as possible. The subcommittees considered the toxicological problems associated with formaldehyde in the areas of exposure, epidemiology, carcinogenicity/histology/genotoxicity, immunology/sensitization/irritation, structure activity/biochemistry/metabolism, reproduction/teratology, behavior/neurotoxicity/psychology and risk estimation. Some questions considered included the possible human carcinogenicity of formaldehyde, as well as other human health effects, and the interpretation of pathology induced by formaldehyde. These reports, plus introductory material on the procedures used in setting up the Consensus Workshop are presented here.

Additionally, there is included a listing of the data base that was made available to the panel chairmen prior to the meeting and was readily accessible to the participants during their deliberations in the meeting. This data base, since it was computerized, was also capable of being searched for important terms. These materials were supplemented by information brought by the panelists.

The workshop has defined the consensus concerning a number of major points in formaldehyde toxicology and has identified a number of major deficits in understanding which are important guides to future research.

Introduction

Background

At the request of the White House Office on Science and Technology Policy (OSTP), the Environmental Protection Agency (EPA) has worked with the National Center for Toxicological Research (NCTR) to conduct a Consensus Workshop on Formaldehyde. This workshop is part of the NCTR Consensus Workshop Series, which continues the commitment of addressing today's important and often controversial toxicological issues. This series is an evolving process where scientists from academia, government, industry, and public interest groups can meet and resolve scientific questions on the basis of the best science currently available. Since this is a relatively new approach to toxicological questions, the "workings" of the workshop will be explained in some detail in an effort to give a clear understanding of the process and, hopefully, provide some insight into how future workshops can utilize the experiences of this one to optimize their chances for success.

History of this Consensus Workshop

Upon the determination of OSTP that it would be useful for a Consensus Workshop to convene and attempt to resolve some important controversies concerning the scientific status of formaldehyde,the EPA and NCTR entered into an Interagency Agreement, which determined that an Executive Panel, drawn from academia, government, industry and public interest groups, would be appointed and provide direction to the workshop. This direction consisted of: (1) defining the format of the workshop, which eventually consisted of eight separate panels; (2) determining the topics, in the

* Executive Panelists (the workshop's executive panel, whose members provided direction to the Consensus Workshop on Formaldehyde and coordinated this report): Michael Gough (Office of Technology Assessment, Congress of the United States, Washington, DC 20510); Ronald Hart (Consensus Workshop Chairman, National Center for Toxicological Research, Building 13, Room 123c, Jefferson, AR 72079); Bruce W. Karrh (E.I. du Pont de Nemours & Co., 11400 Nemours Building, Wilmington, DE 19898); Adalbert Koestner (Department of Pathology, Michigan State University, A-622 East Fee Hall, East Lansing, MI 48824); Robert Neal (Chemical Industry Institute of Toxicology, P. O. Box 12137, Research Triangle Park, NC 27709); David Parkinson (University of Pittsburgh, School of Medicine, Department of Occupational and Environmental Health, Pittsburgh, PA 15213); Frederica Perera (Natural Resources Defense Council, 122 East 42 St., New York, NY 10168) (present address: Columbia University School of Public Health, Division of Environmental Health Sciences, 60 Haven Ave., New York, NY 10032); Kenneth E. Powell (Centers for Disease Control, 1600 Clifton Rd., Atlanta, GA 30333); Herbert S. Rosenkranz (Center for the Environmental Health Sciences, Case Western Reserve University, School of Medicine, Cleveland, OH 44106). The names of the authors are in alphabetical order. These affiliations are for identification only and should not be in any way construed as representing the official opinion or position of any organization. Document editors were Ronald W. Hart, Angelo Terturro and Lorraine Neimeth; William F. McCallum was Workshop Executive Secretary.

form of questions, which focused the discussion; (3) selecting the experts in the various fields to comprise the section panels; and (4) choosing the section chairman and alternate chairman of each panel.

Three months before the meeting, the chairman of the Executive Panel notified the chairmen of the various sections that a compilation of all current information on formaldehyde, both published and unpublished literature, was available. The compilation was able to be searched by keywords, permitting the massive amount of material to be amenable to analysis. This data base (Appendix I) was also available at the Consensus Workshop, as were copies of whatever reprints were required by the panel members.

Workshop Ground Rules

Before the meeting, the chairman of the Executive Panel and the section chairmen discussed the role of the section chairmen and what was expected in terms of the report from each section. Ground rules established by the Executive Panel for conducting the workshop were as follows.

(1) Each panel's report was to focus on those areas where consensus was reached on an issue by the panel, including the major considerations and factors in reaching agreement. Other general ideas, as well as special issues where consensus was not reached, were to be listed and the scientific basis preventing consensus stated.

(2) Reaching consensus does not mean formal voting. Instead, the chairman was to guide the discussion in an effort to get agreement of all members of the panel on each topic of discussion—asking at the end whether there is a consensus.

(3) The alternate chairman/secretary was to take notes during the panel meetings. The chairman was to have the responsibility for submission of the panel draft reports in time for typing and prior to the Wednesday morning session.

(4) The draft report from each working group was to be reviewed by each member of that panel. Ideally, each panel's report was to be drafted and reviewed by every member before leaving the workshop. If this was not accomplished, a draft was to be sent to each panel member for comment. If a second draft were to be necessary, the same procedures would be followed.

(5) Written comments or requests to present information/data from the floor were to be received by the panel chairman for consideration and inclusion in the panel deliberation. No other comments were to be accepted.

(6) Executive Panel members were not to revise or edit the working group reports. Their duties were: (a) to read each panel's report and to identify either areas requiring clarification or inconsistencies between various panels' findings so that the chairmen of the relevant panels could attempt to correct these problems and (b) to write a short introduction explaining the purpose of the workshop and the process followed in selecting topics and participants as well as in discussing topics. The conclusions of each working group were to speak for themselves and not require interpretation, summary or introduction.

(7) In the final document, a disclaimer was to be cited that the statements contained therein should in no way be construed as representing the official opinion or position of any agency, organization or institution to which participants in the workshop belong.

(8) The findings of the Risk Estimation Panel were to be circulated to all panelists for evaluation and comment, with a turnaround time not to exceed three weeks. The Risk Estimation Panel was then to have the responsibility for final drafting of their report based on their deliberation and the comments from the other panelists.

(9) During the deliberation of the Risk Assessment Panel, the chairperson or designate was to report only the findings of the panel as a whole. If a panel chairman or designate were to have a personal comment, he/she could notify the chairman of the Risk Assessment Panel in writing as was the case for any other member of the panel and the audience.

(10) The Risk Assessment Panel report was to be bound by the consensus findings of the panels. Valid scientific disagreements within the panel were to be treated as stated in item (1) above.

Workshop Foci

Recent scientific studies have heightened concern about the possible human health effects of formaldehyde. The data relating to some of these health effects have been reviewed by governmental, independent and international panels of scientists. These reviews of the formaldehyde data have resulted in regulatory actions or proposals by several federal agencies; however, controversy remains over a number of scientific issues. At the request of the Regulatory Work Group on Science and Technology, White House Office of Science and Technology Policy, the National Center for Toxicological Research (NCTR) convened a scientific consensus workshop on formaldehyde to discuss and seek general agreement on the existing scientific data and identify future research needs.

The Consensus Workshop on Formaldehyde met and discussed in an objective and nonadversarial fashion the relevant scientific evidence on formaldehyde in the general areas of epidemiology, exposure, toxicology and risk estimation. The endpoints discussed for each of the above general areas could include, but were not restricted to: carcinogenicity, genotoxicity, irritation, reproductive effects/teratology, behavioral effects, immunotoxicology/sensitization, neurotoxicity, biochemical effects/metabolism and histopathological effects. The emphasis of the workshop was to develop consensus on the scientific issues concerning formaldehyde; however, the results may also be used to assist in future regulatory decision making.

Because of the wide variety of information available within a topic, the nature of the area addressed and difference in the scope and depth of the questions, the different panels chose to present the answers differently. Some panels gave answers directly, others decided to present the response in a narrative form. To preserve the nuances and subtleties of the different panels of experts, there has been no editing of the panel reports, other than that required for journal publication. This led to some significant differences in the style, pacing and flow of the narrative.*

Workshop Orientation

Each panel specifically concentrated on the "science" and the scientific questions of numerous issues concerning formaldehyde and deliberately avoided philosophical, policy and/or regulatory aspects. Despite the organizational difficulties in obtaining a "balanced input" from divergent scientific viewpoints, the workshop demonstrated that, in considering science issues with give-and-take discussion, many of the differences have been significantly narrowed and consensus reached on many important toxicological issues. It is hoped that this workshop has been instrumental in updating and synthesizing the scientific data on formaldehyde and strengthening the factual basis for environmental health risk assessment of this substance.

Each panel prepared and reviewed a report from its deliberations, and the chairmen of each panel presented the reports to the workshop in plenary session. The panel reports follow in their entirety. Because of the density of information, complexities, and variances of the panel reports, the Executive Panel decided not to attempt further summarization.

Exposure Panel Report†

Topic 1. What are the sources, modes and levels of exposure in various segments of the population?

a. What are the available monitoring (collection and analytical) methods and what are the reliability, accuracy, sensitivity, specificity, comparability and limitations of these methods?
b. What is known about the levels and sources of exposure in residences, public buildings, occupational areas, outdoor air, water, soil, consumer products and medical procedures? How do these exposures vary in duration, concentration and frequency?
c. What factors (environmental and physiological) affect exposure in man and experimental animals?
d. What is the size and composition of populations exposed to various ranges of concentrations of formaldehyde by various routes?

Topic 2. What data that are currently lacking would be most important in resolving controversies about exposure?

Topic 1: Sources, Modes and Levels of Exposure

1a. Many methods have been used for measuring formaldehyde levels in air and other media. A selection of these methods has been critically reviewed by Balmat (*1*) for the Formaldehyde Institute. The information in Table 1 has been extracted and condensed from this review to provide a concise summary of the 19 methods that provide the basis for the monitoring data reviewed by the panel. To facilitate comparisons, columns 4 and 5 in Table 1 provide estimates of the sensitivity of each method for short-term (15-min) and long-term (usually 8-hr) sampling (devices intended for sampling over periods of several days may achieve higher sensitivities than those listed in Table 1). These reported sensitivities do not necessarily represent values measured using standard test atmospheric concentrations, but are calculated from reported limits of quantitation, assuming recommended sampling rates. The last two columns list the main advantages and disadvantages of each method, including known interferences, classified as positive (+) or negative (-) where appropriate. Criteria for precision and accuracy of each method have been established (*1*). However, these criteria are valid only when the methods are used according to their written procedures, and deviations from these procedures in sample collection or analytical procedures can greatly influence the precision and accuracy of any procedure.

Evaluation of the reliability of monitoring data requires critical assessment of the methodology used for sampling and analysis and of the interfering compounds likely to be present. As shown in Table 1, each method has advantages and disadvantages. Choice of an inappropriate method, improper conduct of the sampling or analysis, or the presence of interferences may lead to substantial positive or negative biases.

In the judgment of the panel, adequate methods exist for both short-term and long-term monitoring of formaldehyde concentrations in a variety of conditions, including occupational and residential situations. A number of these methods have been standardized and evaluated under laboratory conditions. However, panel members expressed concern about several aspects of published formaldehyde studies: (a) some reports included inadequate or no documentation of the methods used; (b) some studies involved inappropriate choice or improper modification of methods; (c) some methods (e.g., passive monitors) are coming into widespread use without complete evaluation under field conditions. For this reason, some studies probably have achieved substantially less precision and accuracy than claimed for the

* Italic number/letter designations (e.g., *2a*) refer to the specific topic areas; the same number is used more than once if the discussion again becomes relevant to a particular topic.

† Exposure Panel: Ian Nisbet (Chairman); Bernd Seifert (Alternate Chairman/Secretary); Jean L. Balmat; John M. Fajen; Richard Gammage; Eugene R. Kennedy; Michael Silverstein.

Table 1. Sampling and analytical methods for formaldehyde.[a]

Method designation	Analytical technique		Sensitivity, ppm		Advantages	Disadvantages
	Sampling	Analysis	15 min	Long-term		
Chromotropic acid, P&CAM 125	Midget impinger	Spectrophotometry	0.16	0.04 (1 hr)	Sensitive and selective, simple technique	Interferences: phenol (−), other organics (−)
Paraosaniline, original	Midget impinger	Spectrophotometry	0.02	0.0005 (8 hr)	High sensitivity, simple technique	Interferences: SO_2 (+), uses toxic materials, uses double impingers, poor sample stability
Pararosaniline, modified	Midget impinger	Spectrophotometry	0.045	0.001 (8 hr)	High sensitivity, simple technique, uses no Hg compound	Interference: SO_2 (+), uses double impingers, poor sample stability, results are temperature dependent
Pararosaniline, TGM-555	Continuous	Colorimetric	0.05	NA	High sensitivity, near real-time monitoring	Interference: SO_2 (+), uses toxic materials, time consuming and involved maintenance
MBTH	Absorber	Spectrophotometry	0.10	0.003 (8 hr)	Simple, good sample stability	Poor specificity
Acetylacetone, spectrophotometric	Midget impinger	Spectrophotometry	0.10	—	Mild pH, sensitive and simple technique	Interferences: other aldehydes (+), amines (−), SO_2 (−), unstable chromogen
Acetylacetone, fluorimetric	Midget impinger	Fluorimetry	0.04	—	Mild pH, sensitive and simple technique	Interferences: other aldehydes (+), amines (−), SO_2 (+), unstable chromogen
2,4-DNPH, aqueous ethanol	Midget impinger	HPLC	0.00006	0.000015 (1 hr)	Sensitive, specific, good collection efficiency	High level of analytical sophistication
2,4-DNPH coated adsorbent	Adsorbent tube	HPLC	1.32	0.10 (3 hr)	Specific, solid adsorbent	High level of analytical sophistication, user must prepare tubes, short shelf-life, variable blank level, poor sensitivity
P&CAM 318	Reactive adsorbent	Ion chromatography	0.8	0.025 (8 hr)	Specific, solid sorbent	High level of analytical sophistication, poor sample stability, interferences: formic acid (+), variable recovery
NIOSH S327	Midget impinger	Polarography	1.62	0.27 (1.5 hr)	Few steps in procedure, stable sample	High level of analytical sophistication, poor sensitivity, interference: other aldehydes (+)
OSHA, acidic hydrazine	Midget impinger	Polarography	0.10	0.01 (2.5 hr)	Sensitive	High level of analytical sophistication, interference: acetaldehyde (+), high blanks
P&CAM 354	Reactive adsorbent	Gas chromatography	7.32	0.5 (4 hr)	Selective, sorbent tube, stable sample	High level of analytical sophistication, poor sensitivity
MIRAN	Continuous	Infrared	0.4	NA	Real-time analysis	Subject to multiple interferences (+)
Draeger	Reactive adsorbent	Visual	0.5	NA	Real-time analysis	Questionable accuracy and precision
Passive monitor						
3 M	Reactive adsorbent	Spectrophotometry (CA)	3.2	0.1 (8 hr)	Ease of sampling	Sensitive to humidity and face velocity
DuPont	Reactive adsorbent	Spectrophotometry (CA)	8	0.25 (8 hr)	Ease of sampling, simple analytical procedure	Poor sensitivity, variable blanks
Air Quality Research	Reactive adsorbent	Spectrophotometry (CA)	6.7	0.21 (8 hr)	Ease of sampling	Limited shelf life, results sensitive to humidity
Envirotech	Moist adsorbent	Spectrophotometry (PUR)	0.72	0.06 (3 hr)	Ease of sampling	Results not easily interpreted, color reagent unstable, turbidity correction, interferences: other aldehydes (+)

[a](CA)–chromotropic acid; (PUR)–Purpald.

methods. In general, negative biases (due to interferences and sample instability) are likely to be more frequent than positive biases. However, in the panel's judgment, these errors are probably less serious than errors introduced by the inadequacies and biases in sampling that are discussed below.

Methods for biological monitoring of exposure to formaldehyde by measuring increases in concentrations of formate in urine have been proposed (*2–4*). However, natural variability in formate levels is too high for these methods to be useful except in populations exposed to ambient formaldehyde levels greater than 1 ppm.

1b. Occupational Exposure. The panel reviewed four surveys and compilations of data on occupational exposure to formaldehyde as well as a number of primary studies. The largest single source of data is a study conducted for the Synthetic Organic Chemical Manufacturers' Association (SOCMA) (*5*), in which 50 industries with the potential for significant worker exposure to formaldehyde were identified and 17 industries were surveyed. Company monitoring data were tabulated for 10 industries and estimates were made of the frequency and range of exposures in all 17 industries. However, the utility of this information is severely limited since only 89 of the 3365 companies to which questionnaires were sent provided monitoring data, and the report did not specify the methods of analysis or the circumstances in which the data were collected. For these reasons, the panel felt that these data could not be scientifically evaluated. The panel also excluded from its review several other studies for which methods of analysis or other critical pieces of information were omitted.

Table 2 summarizes the remaining data available to the panel. Many of these data have previously been compiled by the U.S. Environmental Protection Agency (*6*) and Clement Associates (*7*). We have added results from recent studies by the National Institute for Occupational Safety and Health (NIOSH) (*8*) and several additional published reports. The compilation by Hattis et al. (*9*) was not available to the panel.

The panel regards the ambient monitoring data summarized in Table 2 as reasonably reliable measures of the concentrations of formaldehyde in the workplaces that were sampled, except for measurements made by the charcoal tube (CT) method, which are especially subject to negative bias. Thus, at least at the time of sampling, the data indicate substantial exposure of workers to formaldehyde in several industries. Specifically, sample means of 1 ppm or more have been reported in the following industries and occupations: formaldehyde production; resin and plastic materials production; apparel manufacture; plywood particle board and wood furniture manufacture; paper and paperboard manufacture; urea–formaldehyde foam insulation (UFFI) dealers and installers; mushroom farms; funeral services; and pathological and biology laboratories. High concentrations of formaldehyde have also been reported in individual samples from iron foundries and plastic molding facilities. However, the panel notes that published data are available for only 34 job categories in 29 industries and occupations. For no job category are the data sufficient to characterize temporal or within-plant variability, or to characterize exposure in more than a small handful of plants. Hence, the panel concludes that the available data, although useful in showing the range of exposures encountered in some workplaces, are not sufficiently systematic or representative to characterize the entire spectrum of exposures in U.S. industry.

In addition to the data summarized in Table 2, the SOCMA (*5*) survey suggested that substantial exposure to formaldehyde also occurs in several other industries, including industrial and specialty chemicals and manufacture of hardwood plywood, particleboard and abrasive products. In addition, both the SOCMA survey and the National Occupational Hazard Survey (*35*) identified a number of other industries with potential formaldehyde exposures, for which the panel has not encountered any monitoring data.

1b. Indoor Exposure. Table 3 summarizes data from six studies of formaldehyde levels in residences in different parts of the United States, Canada and the United Kingdom. Although there is some question about the randomness and representativeness of some of the samples, the panel judges that the mean levels from the large-scale studies whose results are tabulated in Table 3 provide reasonable estimates of the long-term average concentrations of formaldehyde in various broad categories of housing types.

In conventional homes more than about five years old, mean concentrations of formaldehyde are usually below 0.05 parts per million (ppm), and only a small fraction exceeds 0.1 ppm (the American Society of Heating, Refrigeration and Air-Conditioning Engineers [ASHRAE] ceiling guideline for comfort and the standard established in several foreign countries). In specialized residences (mobile homes, UFFI homes, new houses, energy-efficient and perhaps weatherized homes), mean levels of formaldehyde are significantly higher and not infrequently exceed 0.1 ppm. Mean levels appear to be highest in mobile homes (Table 3).

Levels of formaldehyde are highest in new residences and decline steadily as the rates of emission from insulation or building materials decline. The first half-life is 4 to 5 years for mobile homes and for new houses (*39*) where pressed-wood products are the primary source of formaldehyde. For UFFI homes the first half-life is usually less than 1 year (*41,42*).

Although mean formaldehyde levels in different classes of residences are reasonably well established, temporal patterns of fluctuation are poorly characterized and not well understood. The cross-sectional studies in Table 3 were not designed to investigate patterns of variability, and the ranges cited there reflect both between-house differences and within-house variations. Limited studies of within-house fluctuations (*43,44*) have revealed both diurnal variations (up to twofold) and seasonal variables (up to tenfold in some homes). Highest levels occur in the summer and in the heat of

Table 2. Formaldehyde monitoring data in occupational settings.

Industry	Job	Exposure levels, ppm			Sampling methods					Ref.	Comments
		Range	Mean	Median	Area or pers.	No. obs.	Period	Methods[a]	Duration/ frequency		
Formaldehyde production (SIC 2869)	Production operators	—	1.4	—	P	—	4 hr TWA	CT,IC	—	(*10*)[b]	
	Lab tech	—	1.31	—	P	—	4 hr TWA	CT,IC	—	(*10*)[b]	
Resin and plastic materials production (SIC 2821)	Production operators	—	1.39	—	P	—	4 hr TWA	CT,IC	—	(*10*)[b]	
	Resin plant	0.05–0.37	0.24	—	A	8	—	BI,CT GC	—	(*11*)[b]	
	Resin plant	0.09–0.17	0.13	—	A	2	405 min	BI,CO	Intermittent	(*12*)[b]	Manufacture glue for plywood, samples taken over glue vat
	UF resin production (2 plants)	0.12–0.55	—	—	A	—	—	SS,IC	—	(*13*)	Resin production
		0.18–5.4	—	—	A	—	—	SS,IC	—		Resin drumming
		0.2–0.74	—	—	A	—	—	SS,IC	—		Drum washing
		0.6–0.34	—	—	A	—	—	SS,IC	—		Foam agent blending
	UF resin production	0.12–5.4	0.90	—	P	18	—	BI,CA	—	(*14*)[b]	Cooks
		0.20–0.74	0.39	—	P	5	—	BI,CA	—		Drum washer
		0.06–0.34	0.19	—	P	5	—	BI,CA	—		Foaming agent blender
Textile finishing (SIC 226-)	Textiles warehouse	0.04–0.73	0.31	—	A,P	11	—	CT,SP	—	(*15*)[b]	
		0.08–0.51	0.25	—	A,P	11	—	BI, SP	—		
	Textile facilities	< 0.1–1.3	—	0.8	A,P	28	—	—	—	(*16*)[b]	
		< 0.1–1.4	—	0.7	A,P	15	—	—	—		
	Textile manufacture	0.11–1.33	0.69	0.64	P	6	+3 hr	—	8 hr/day	(*17*)	
		0.15–1.2	0.53	0.45	A	13	Grab	—	—		
Apparel (SIC 23-)	Permanent press	0.15–0.38	0.31	—	A	9	—	BI,I	—	(*18*)[b]	Early date; area samples taken in workroom
	Permanent press	0–2.7	0.74	—	A	32	—	BI,I	—	(*19*)[b]	Early date; area samples taken in cutting, pressing, sewing, and storage areas
	Warehouse	0.11–0.57	0.39	0.37	P	13	30–45 min	—	8 hr/day	(*15*)	
		0.04–0.19	0.12	0.15	A	9	164–341 min				
	Sewing machine operators	0.51–0.91	0.72	0.71	P	16	7–8 hr	—	8 hr/day	(*15*)	
		0.3–1.8	1.2	1.2	P	41	30 min	—			
	Clothing pressers	0.005–0.95	0.07	0.054	P	40	3–4 hr	—	8 hr/day	(*20*)	
Plywood particle-board (SIC 243-)	All workers	—	1–2.5	—	A	—	—	—	—	(*16*)[b]	
Wood furniture manufacture (SIC 2511, 2512, 2521, 2531, 2541)	Particle-board veneering	0.008–0.25	0.12	—	A	11	—	BI,CA	—	(*13*)	Plant
		0.9–6.4	2.75	—	A	—	—	BI,CA	—		Veneer press
		0.2–0.55	0.40	—	A	9	—	BI,CA	—		Veneer core press
		0.2–2.5	0.70	—	A	13	—	BI,CA	—		Core, veneer, adhesives
Plastic molders (SIC 3079)	Injection mold operators	0.01–0.1	0.037	—	P	9	100–350 min	CA	—	(*21*)	Breathing zone samples

Table 2. (continued)

Industry	Job	Exposure levels, ppm			Sampling methods					Ref.	Comments
		Range	Mean	Median	Area or pers.	No. obs.	Period	Methods[a]	Duration/ frequency		
Plastic molders (sic 3079) (cont'd)	Area samples	0.01–0.53	0.20	—	A	8	55-425 min	CA	—	(*21*)	Area samples
	Operators	< 2	< 2	< 2	P	28	—	DT	—	(*21*)	Breathing zone samples; limit of detection is 2 ppm
	Near grinder hopper	2–4	3	3	A	3	—	DT	—	(*21*)	Wear machines processing acetal resins
	Sand mold production	0.1–0.7	0.31	0.2	P	28	4 hr	—	8 hr/day	(*22*)	
		ND–1.1	0.17	0.1	A	29	4 hr	—			
Paper and paperboard (SIC 26-)	Paper treatment resin impregnated)	0.04–0.16	0.08	—	P	15	4 hr	BI,CT CA	8 hr/day	(*11*)	Filter treating of paper
		0.03–0.07	0.06	—	A	7	4 hr	BI,CT CA	8 hr/day		Filter treating of paper
		0.01–0.23	0.05	—	P	30	4 hr	BI,CT CA	8 hr/day		Series B collating
		0.02–0.28	0.05	—	P	10	4 hr	BI,CT CA	8 hr/day		Press build-up
	Treated paper products	0.14–0.99	—	0.59	A	64	—	—	—	(*16*)[b]	
		0.14–0.90	—	0.34	P	37	—	—	—		
	Coating preparation	< 0.01–3	1	0.01	A	7	Grab	—	ca. 30 sec 20 times/day	(*23*)	By mix and storage tanks; data indicated no exposure in work area where majority of work time spent
		0.8–0.42	0.51	0.42	A	4	30-200 min	—			
Foundries steel, iron and nonferrous (SIC 332-, 336-)	Bronze foundry, core machine operators	0.24–0.80	0.53	0.55	P	4	3–4 hr	BI,CA	8 hr/day	(*24*)	
		0.12–0.69	0.39	0.39	A	11	ca. 2 hr	BI,CA	—		
	Iron foundry, core machine operators	< 0.02–18.3	—	0.43	P	14	—	—	—	(*16*)[b]	
	Iron foundry, core machine operators	0.07–0.33	0.16	—	P	3	—	BI,CA	8 hr/day	(*25*)	Complete core production cycle took 1 hr
	Molding	0.03–0.13	0.09	—	P	6	—	BI,CO	—	(*26*)	Molding for products to measure temperature, PF resins
		0.07–0.78	0.21	—	A	6	—	BI,CO	—		
Rubber hose production (SIC 3069)	—	ND–0.04	0.04	—	P	10	—	BI,CO	—	(*27*)[b]	Formaldehyde used as a preservative
Asphalt shingle production (SIC 2952)	Producers	0.03–0.07	0.05	0.05	A	2	—	BI,CO	—	(*28*)[b]	Area samples near process machinery
Fiberglass insulation installation (SIC 3296)	Installers	0.007–0.033	0.023 (TWA)	0.019	P	13	—	—	8 hr/day	(*29*)	Rapid worker turnover rate reported, with most employees leaving within 6 mo

Table 2. (continued)

Industry	Job	Exposure levels, ppm			Sampling methods					Ref.	Comments
		Range	Mean	Median	Area or pers.	No. obs.	Period	Methods[a]	Duration/ frequency		
Urea–formaldehyde foam insulation dealers and installers	See comments	0.07–2.0	—	—	—	—	—	IC	—	(*13*)	Application of UF foam to commercial and residential buildings; exposures for applicators, laborers, trucking, and warehouse area
	Suburban shopping center insulated with UF foam	0.8–1.6	1.05	—	A	36	—	BI,CA	—	(*16*)[b]	Area samples in stores
		0.3–3.1	1.44	—	A	30	—	CT,IC	—		
		< 0.5–3.0	1.56	—	A	16	—	DT	—		
Fertilizer manufacturers (SIC 2873)	—	0.2–1.9	0.9	—	P,A	11	—	—	—	(*16*)[b]	For production of time-released nitrogen fertilizers (urea forms), release formaldehyde as they release nitrogen
Mushroom farm (SIC 0721)	—	< 0.51–10+	2.68	—	A	12	—	DT	Intermittent	(*30*)[b]	Maximum value was sample taken at source; formaldehyde used as fumigant/ disinfectant
		ND–2.70			P	3	Short-term	CT,IC	Intermittent		
		ND–4.93	—	—	A	3	—	CT,IC	Intermittent		
Funeral homes (SIC 7261)	Embalmers	0.09–5.26	0.74	—	A	187	—	CA	—	(*31*)	Wayne State University study of 6 funeral homes; mean concentration increased to 1.34 ppm when ventilation off
	Embalmers	0.20–3.99	1.1	0.54	A,P	8	70–190 min	CT	—	(*32*)[b]	Area and personal samples; ventilation working
		1.30–3.93	2.7	2.49	A,P	5	300 min	CT	—		Area and personal samples; ventilation inoperative
Pathologists (SIC 8071)	Autopsy room	0.06–7.9	4.8	—	A	10	—	BI,CA	Intermittent	(*33*)[b]	
	Autopsy room	2.20–7.9	4.35	—	A	6	—	—	Intermittent	(*16*)[b]	
Biology instructors (SIC 8071)	Biology lab	2.75–14.8	8.3	—	A	8	—	BI,CA	Intermittent	(*6*)	Minimum concentrations with doors and windows open; maximum concentrations with doors and windows closed; 18 dissected cats saturated with formalin in room

Table 2. (continued)

Industry	Job	Exposure levels, ppm			Sampling methods					Ref.	Comments
		Range	Mean	Median	Area or pers.	No. obs.	Period	Methods[a]	Duration/ frequency		
Hospital	—	2.2–2.3	2.25		P	2	—	BI	—	(*8*)	
lab		1.9			P	1	—	CT	—		
(SIC 8071)		2.0–2.0	2.0		A	2	—	CT	—		
Government	—	2.4	—		P	1	—	CT	—	(*8*)	
lab		0.8	—		A	1	—	CT	—		
(SIC 8071)											
Dialysis	—	ND–0.90	0.42		A	9	—	CT	—	(*8*)	
unit		0.27–0.63	0.41		P	5	—	CT	—		
(SIC 8081)		0.04–0.50	0.51[b]		A		—	CEA	—		
Animal	—	< 0.38–1.04	—		P	15	—	CA	—		
dissecting		0.05–0.40	0.15		A	6	—	BI	—		
lab		0.11–0.29	0.18[b]		A	3	—	CEA	—		
(SIC 8071)											
Garment	—	< 0.14–0.63	0.23–0.33		P	40	—	CT	—	(*8*)	
manufactur-		< 0.03–0.40	0.19–0.26		A	43	—	CT	—		
ing (3 plants)		0.03–0.40	0.21		A	43	—	BI	—		
(SIC 2321)		0.05–1.12	0.46		A	42	—	CEA	—		
Chemical	—	0.04–1.6	0.55	—	P	3	—	BI	—	(*8*)	
manufac-		0.03–0.43	0.17	—	A	5	—	BI	—		
turing											
Glass	—	0.42	0.42	—	P	1	—	CT	—	(*8*)	
manufac-		0.45–0.64	0.54	—	A	2	—	CT	—		
turing											
(SIC 3211)											
Hospital	—	0.37–0.73	0.55	—	A	2	—	BI	—	(*8*)	
(SIC 8062)											
Paraformal-	—	< 0.25–0.85[b]	0.56[b]	—	P	10	—	CA	—	(*8*)	
dehyde		0.28–3.40	1.17[b]	—	A	8	—	CEA	—		
packaging											
(SIC 2879)											
Offices	—	0.02–0.12	0.06	—	A	39	—	BI	—	(*8*)	
(3 locations)		< 0.04	< 0.04	—	A	9	—	CT	—		
(SIC 8111)											
Autopsy	Resident	—	1.58[c]		P	10	—	CA	—	(*4*)	
rooms											
(SIC 8071)	Pathologist	—	1.24[c]		P	10	—	Ca	—		
	Technician	—	0.57[c]		P	9	—	CA	—		
	Assistants	—	0.16[c]		P	2	—	CA	—		
		0.13–13.57	0.72		A	23	—	CA	—		

[a]Abbreviations for analytical procedures: AA = acetylacetone procedure; BI = bisulfite impingers; CA = chromotropic acid procedure; CL = chemiluminescence procedure; CO = colorimetric analysis; CT = charcoal tubes; SS = solid sorbents; DT = Draeger tubes; FS = Fourier transform spectrometer; GC = gas chromatography; IC = ion chromatography; MB = MBTH procedure; SP = spectrophotometric procedure; CEA = CEA instruments Model 555.

[b]As reported by USEPA (*6*).

[c]Average.

the day; doubling of formaldehyde levels has been observed with temperature increments of 3–8°C (*39*,*45*). In an intensive study, over a period of 1 year, of 40 homes, more than half of which were less than 5 years old, a level of 0.1 ppm was exceeded in more than half the homes during at least one 24-hr period (*39*). However, the panel judged the available data inadequate to characterize the frequency or magnitude of short-term peak (acute) exposures of various groups within the population.

The information provided by past surveys is limited by failure to standardize or report sampling design or details of protocols, such as location and timing of samples, ventilation rates, human activity, etc. Sampling of nonresidential indoor environments, such as offices, public buidings, schools, retail stores, and vehicles, has been sparse.

Indoor sources of formaldehyde have been identified both by association with high ambient levels and by direct measurement of emission rates. The strongest sources are articles fabricated with urea-formaldehyde resins that are used in large amounts in the indoor environment. Examples include UFFI, hardwood plywood (decorative) paneling, and particleboard underlays or decking. Medium-density fiberboard is a sufficiently strong emitter (*46*) that even smaller articles such as furniture can elevate indoor levels of formaldehyde significantly (*38*). Transient increases in formalde-

Table 3. Reported levels of formaldehyde in indoor air in residences.

Type of residence	No. of residences	Formaldehyde, ppm Range	Mean	Reference
House without UFFI[a]	41	0.01–0.1	0.03	(*36*)
House with UFFI (complaint and non-complaint)[b]	636	0.01–4	0.12	(*36*)
Houses without UFFI	378	(3% > 0.1 ppm)	0.035	(*37*)
House with UFFI (complaint and non-complaint)[b]	1146	(10% > 0.1 ppm)	0.054	(*37*)
Mobile homes	431	0.01–3	0.38	(*38*)
Mobile homes (Washington, complaint)[b]	—[c]	0–1.77	0.38	(*38*)
Mobile homes (Minnesota, complaint)[b]	—	0–3.0	0.4	(*38*)
Mobile homes (Wisconsin, complaint)[b]	—	0.02–4.2	0.9	(*38*)
East Tennessee homes	40	< 0.02–0.4	0.06	(*39*)
Age 0–5 yr	18		0.08	(*39*)
Age 5–15 yr	11		0.04	(*39*)
Age >15 yr	11		0.03	(*39*)
California, Colorado and S. Dakota homes (conventional)	64	0.02–0.11	0.05	(*40*)
California homes (mobile, energy-efficient, weatherized)	52	0.03–0.3	0.1	(*40*)
U.K. buildings without UFFI	50	< 0.02–> 0.3	0.047	(*41*)
U.K. buildings with UFFI	128	0.01–> 1	0.093	(*41*)

[a]UFFI: urea–formaldehyde foam insulation.
[b]Complaint: homes in which residents had complained of symptoms putatively associated with exposure to formaldehyde.
[c]Number not stated.

hyde levels can also be caused by burning cigarettes or gas-fired space heaters. In extreme cases (heavy smoking or poorly tuned heaters), these transient increases can exceed 0.1 ppm (*47*).

1b. Environmental Exposures. Environmental levels of formaldehyde have been summarized by the National Research Council (NRC) (*38*) and other reviewers. Concentrations reported in ambient air have generally been below 10 to 15 parts per billion (ppb), except for situations of heavy traffic and/or photochemical smog, when concentrations up to 90 to 150 ppb have been reported (*38,48*). These urban concentrations appear to have decreased since the 1960s (*38,48,49*) and are likely to decrease further as automobile emissions are progressively reduced. Rain water in Western Europe contained 0.3 to 1.4 μg/L formaldehyde in 1969 and 0.1 to 0.17 μg/L formaldehyde in the mid-1970s (*49*). The panel has not reviewed these data in detail because outdoor exposures appear to be much smaller than indoor exposures.

1b. Consumer Products and Medical Devices. Table 4 lists data on the occurrence of formaldehyde in consumer products, drugs, and disinfectants. Formaldehyde is used quite widely in cosmetics and household disinfectants. However, the panel was not able to find any data on the extent of exposure to these products via skin contact or inhalation. Formaldehyde is also used to disinfect medical devices such as kidney dialysis units, giving rise to potential exposures of users and medical personnel. The panel was concerned about a report from Europe of high concentrations (up to 15–25 ppm) of formaldehyde in incubators used for intensive care of premature infants (*53*).

Table 4. Formaldehyde in consumer products and medical products.

Type of product	Formaldehyde content, %	Reference
Household products	up to 1%	(*50*)
Household disinfectants (diluted for application); U.S. labeling required at > 1%	up to 7%	(*50*)
Cosmetics (used as preservatives and in shampoos; FDA 1981 listed 805 products containing formaldehyde)	generally < 1% (1% of products in range 1–10%)	(*51*)
Level recommended by CTFA	< 0.2%	(*51*)
Highest permitted content in EEC (except fingernail hardener at 5%); EEC labeling required at 0.05%	0.2%	(*52*)
Disinfectants for medical use		(*50*)
Concentrates	Mostly 5–10% (range: 1–30%)	(*50*)
Diluted for use	< 1%	

1c. The principal physiological factor affecting respiratory intake of formaldehyde is the breathing rate (minute volume), which is dependent on physical activity and is higher (per unit of body weight) in children

Table 5. Extent of exposure to formaldehyde in 23 industries and occupations in the U.S.

Industry (SIC code)	Workers exposed	
	Type (full/part-time)	No.
Formaldehyde production (SIC 2869)	Full	271–913[a]
	Part	145–487[a]
Resin and plastic materials and manufacture (SIC 2821)	Full	4,728
	Part	1,272
Industrial and specialty chemicals and manufacture (SIC 284–, 286–, 287–, 289–)	Full	2,680
	Part	2,220
Paints, dyes, and pigments manufacture (SIC 2851, 2865)	Full	7,480
	Part	29,920
Adhesive and sealants manufacture (SIC 2891)	Full	2,380
	Part	420
Textile finishing (SIC 226–)	Full	17,800
	Part	2,200
Apparel manufacture (SIC 23–)	Full	771,420
	Part	125,580
Hardwood plywood manufacture (SIC 2435)	Full	7,500
Softwood plywood manufacture (SIC 2435)	Full	7,500
Plastic board manufacture (SIC 2492)	Full	2,831
	Part	1,069
Mobile home manufacture (SIC 2491, 2452, 3792)	Full	31,500
Wood furniture (SIC 25–)	Full	47,322
	Part	2,178
Paper and paperboard manufacture (SIC 26–)	Full	6,000–45,000[a]
Plastic molding (SIC 3079)	Full	15,073
	Part	1,527
Abrasive products manufacture (SIC 3291)	Full	3,996
	Part	2,004
Foundries (SIC 332–, 336–)	Full	28,638
	Part	14,362
Producers of rubber and misc. plastic products (SIC 30–)	Full	6,128–27,584[a]
Urea-formaldehyde foam insulation dealers and installers	Full	2,000–15,000[a]
Fertilizer producers (SIC 2873)	Full	500–900[a]
Funeral services (SIC 7261)	Part	52,000–70,200[a]
Pathologists	Part	12,400[a]
Biology instructors (college/university)	Part	13,000[a]
Biology instructors (high school)	Part	22,000[a]
Total for all industries		1,341,084

[a]From USEPA (*6*); all other estimates from SOCMA (*5*).

than in adults. The panel did not review the uptake of formaldehyde through the skin or mucous membranes.

Environmental factors (especially temperature) influencing emission rates of formaldehyde have been discussed in the previous section. Little appears to be known about the physical or chemical form of formaldehyde present in the ambient air. In occupational settings, exposure can be reduced by ventilation and other work practices. The panel found no information on the effectiveness of gloves or other protective clothing.

1d. Occupational Exposures. Table 5 (*54*) lists estimates of the numbers of workers exposed to formaldehyde in 23 industries and occupations in the U.S. For 17 industries, estimates were derived by SOCMA (*5*) on the basis of industry-wide questionnaires. Companies responding to the questionnaires provided data on the number of employees in various job categories potentially exposed to formaldehyde, and these were scaled up to the entire industry, assuming that the proportion of exposed workers was the same in all plants. For six industries and three occupations, estimates were derived by EPA (*6*) by use of data from the Bureau of the Census, from the National Occupational Hazard Survey, and from various assumptions about the number of workers per plant. Except for the Bureau of the Census data on pathologists, the panel regards the EPA data as quite tenuous. The SOCMA data are more soundly based in data from the industries they cover, but are nevertheless subject to substantial biases because of the low response rate (2.7%) to the questionnaire. Thus, except for the estimate for pathologists, each of the estimates in Table 5 could be in error by a factor of up to 2 or 3.

EPA (*6*) cited data from the Bureau of the Census indicating that there are about 1.4 million biology and nursing students in the U.S., most or all of whom are likely to be exposed to formaldehyde intermittently during laboratory studies. Other categories of laboratory workers, such as laboratory and medical technicians, have not been enumerated.

For reasons stated above, it is not possible to break down the occupationally exposed populations according to the levels of their exposure to formaldehyde. The data in Table 5 represent a cross section of industrial populations, and only limited information is available on the duration of their exposure or on rates of job turnover. The number of workers exposed at any one time is only a fraction of the total number of workers exposed during their working lives, but this fraction cannot be estimated from the data available.

1d. Residential Exposures. EPA (*6*) estimated that about 2.2 million persons were living in mobile homes less than five years old and that 1.3 to 1.6 million people were living in homes insulated with UFFI during the preceding five years. The Consumer Product Safety Commission (CPSC) estimated that 1.75 million people were living in homes insulated with UFFI during the preceding 9 years. These estimates were based on construction and installation data and reasonable estimates of family size, and the panel regards them as reasonable. We assume that the remainder of the U.S. population (220 million) is exposed to formaldehyde at levels characteristic of conventional homes (Table 3). For reasons stated above, it is not possible to characterize temporal patterns or short-term peak exposures to formaldehyde.

Topic 2: Currently Lacking Data

2. The panel did not identify substantial controversies about exposure, although a number of gaps and deficiencies in the available data limit the accuracy and completeness of exposure assessment. The most important data needs identified by the panel were the following.

Systematic data are needed on the extent and magnitude of occupational exposure to formaldehyde, including representative, industry-wide information about personal exposures. Priority attention should be given to industries with a large number of persons exposed (e.g., textiles and clothing, and biological laboratories), workplaces with reportedly high concentrations (e.g., foundries and funeral services), and plants in which epidemiological studies are being or have been conducted. An important first step would be systematic compilation and review of data already collected by employers, since the SOCMA (*5*) survey indicated that extensive data already exist in company files.

Systematic data on the variability in concentrations of formaldehyde in indoor air are required to determine the frequency and magnitude of short-term peak exposures. This will require systematic sampling designs, stratified among various categories of houses, with sampling designed to detect both short-term (hourly) and long-term (seasonal) variations. It will also require better standardization of protocols and validation of analytical methods.

Epidemiology Panel Report*

Topic 1. What is the epidemiologic evidence concerning the relationship between formaldehyde exposure and human illness (neoplastic and nonneoplastic)?

a. What are the limitations and/or strengths of the available epidemiologic data (e.g., power, confounding variables)?
b. Can any or all of the data from epidemiologic studies on the relationship between cancer and formaldehyde be combined in order to provide a greater data base for statistical evaluation?
c. Are there any epidemiologic hypotheses that can be developed from case reports of illness following exposure to formaldehyde?
d. What levels of exposure or what types of exposure to formaldehyde have been reliably associated with human biological responses as evidenced from epidemiologic data?
e. Does the epidemiologic evidence indicate that some segments of the population are particularly sensitive to any adverse health effects of formaldehyde? If so, which segments and at what levels of exposure?

Topic 2. After reviewing completed and ongoing studies, what attainable additional studies might clarify any exposure disease relationships?

This report, which discusses the epidemiologic evidence concerning the relationship between formaldehyde exposure and human illness, addresses three issues. First the panel considered the evidence relating to neoplasms; next, nonneoplastic illness; finally, recommendations are made regarding further research directions. The scientific papers published, in press, and in manuscript, that were considered comprise the references. With the single exception of nasal cancer, where case reports are quoted, our discussion is limited to studies in which the material can be related to a definable population. As the Consensus Workshop includes panels on carcinogenicity, biochemistry, exposure and risk estimation, this panel has only to a limited extent attempted an evaluation of the epidemiologic data in the light of other biological information, or in relation to estimates of exposure for different occupations. Nevertheless, whenever possible, qualitative information on level of exposure by occupation was considered.

Topic 1. Formaldehyde and Human Illness

1, 1a. Formaldehyde and Cancer. The plan has been to consider in turn each category of neoplasm to which attention has been drawn in the literature. Most of the studies reviewed use the occurrence of death as the measure of outcome and almost all refer to the

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experience of the adult male working population. This panel considered no evidence relating to persons first exposed in childhood or old age, to women or to the fetus.

1b. As shown in Table 6, information on all sites was not available for all studies. There is a potential problem involved in simply summing observed and expected numbers and then computing an overall observed-to-expected ratio. With this direct summing one or two large studies then provide the weight of evidence. If some unrecognized distortions or biases had affected one or more of these large studies, the summary would also be biased and thus be potentially misleading. Some readers may wish to make their own separate or different summaries using the data. Several summary approaches are possible. For example, a summary could be prepared which omits one (or more) of the separate studies, based perhaps on the quality of the study, geography, etc. The panel advised caution against basing evaluation on the "total" column in Table 7 without considering the inherent differences between the professional and industrial cohorts with regard to exposure and possible compounding factors.

1a, 1b. Although the summary of observed and expected numbers provides a convenient basis for evaluation, it involves a number of important assumptions which limit its validity and usefulness. The bulk of the expected numbers has been calculated on the basis of an analysis of proportionate mortality, and these have been summed with those from studies using other types of data. Some would regard this as inappropriate. Further, it should be emphasized that a substantial proportion of the person-years at risk relates to individuals within the industrial cohorts who were exposed to very low levels of formaldehyde or, as in the case of professionals, who may have been intermittently exposed to higher levels. Historical exposure estimates were made in only two studies (*55,56*). Moreover, in a proportion of men the period between exposure and completion of follow-up has been brief. The overall effect of these factors and of shortcomings in some of the studies is to make interpretation of associations between formaldehyde and cancer difficult. Where such data existed, the induction period was considered (Table 6), since the inclusion of persons with short potential induction times and very low levels of exposure biases the relative risk of the direction of unity. Finally, few studies had information about smoking and all studies lacked data about consumption of alcohol.

The occupations studied fall into two distinct categories and these have been considered separately. The observed and expected cases of cancer in studies of professional people who use formaldehyde in the preservation of human tissues (embalmers, anatomists and pathologists) (*57–63*) are shown separately from those for industrial workers involved in the production and use of formaldehyde. These two groups differ not only in substances other than formaldehyde to which they may have been exposed, but may also differ in the pattern and intensity of exposure to formaldehyde. The panel noted that in industry many of the workers had been exposed for only short periods (i.e., less than one year) while for professional workers the possibility of exposure at varying intervals was present for many years. In addition, personal habits, which almost certainly influence cancer mortality, differ between the professional and industrial groups.

1c, 1d. Selected Sites of Cancer. NASAL CANCER. No case of nasal cancer has been reported in any of the epidemiological studies listed in Table 7 [0 obs; 3.0 exp; 95% confidence limits (CL) for the standardized morbidity ratio (SMR) 0–123] (*55,59,61–63*). This expected figure and, therefore, the confidence interval for the SMR, take no account of induction period or degree of exposure. In other epidemiologic studies of nasal cancer, the evidence suggests that the risk does not begin to rise until 15 to 25 years after first exposure. In a study of British chemical workers (*64*), it can be seen that the study had a 46% chance of detecting a fivefold increase of risk of this rare tumor if risk commenced immediately after the beginning of exposure and was limited to persons exposed to "high levels"; there was only a 28% chance if the risk did not begin to rise until 20 years after first exposure. These data therefore suggest that it is too early to exclude an important increase in risk after a prolonged induction period. In a case-control study of 167 men with nasal cancer carried out jointly in Denmark, Finland and Sweden (*65*) "a scrutiny of occupations for which exposure to formaldehyde possibly may have occurred gave no indication of any association." In a case-control study of 160 patients with nasal cancer in North Carolina and Virginia (*66*) (available for review only in abstract form), no mention was made of any association with formaldehyde.

The panel found two case reports of nasal cancer in persons exposed to formaldehyde. One individual was employed for 25 years in a fabric finishing plant where textiles were permeated with the formaldehyde-based resin. He had previously soldered components of aircraft engines for about 2 years (*67*). Soldering, welding and flamecutting have been associated with an increased risk of nasal cancer (*65*). The second individual had been employed for 32 years at a plant where phenol formaldehyde and formaldehyde resins were manufactured (*68*). As usual, interpretation of these case-reports is problematic.

BUCCAL CAVITY AND PHARYNX. No important excess of cancers of these sites has been observed in relation to the calculated expected numbers in any of the published studies (*55,59–64,69*). In a reclassification of the deaths in the cohort first studied by Marsh there were a total of seven buccal and pharyngeal cancer deaths observed as compared with an estimated 3.1 expected (*68*). Two of these deaths occurred subsequent to Marsh's date of conclusion of follow-up.

BRAIN. A substantial excess of deaths from cancer

Table 6. O/E data by site and by study.[a]

Site	Study	No induction period considered			Induction period considered		
		O	E	O/E	O	E	O/E
Nasal passages							
Professional	Walrath (New York)	0	0.5	0	ND	ND	ND
	Walrath (California)	0	0.6	0	ND	ND	ND
	Stroup	0	0.4	0	ND	ND	ND
	Levine	0	0.2	0	ND	ND	ND
	Harrington	ND	ND	ND	ND	ND	ND
	Matanoski	ND	ND	ND	ND	ND	ND
Industrial	Acheson	0	1.3	0	ND	ND	ND
	Liebling, Marsh	ND	ND	ND	ND	ND	ND
	Tabershaw	ND	ND	ND	ND	ND	ND
	Fayerweather	ND	ND	ND	ND	ND	ND
Buccal cavity and pharynx	Walrath (New York)	8	7.1	1.3	ND	ND	ND
Professional	Walrath (California)	8	6.1	1.6	ND	ND	ND
	Stroup	1	6.8	0.2	ND	ND	ND
	Levine	1	2.1	0.5	ND	ND	ND
	Harrington	ND	ND	ND	ND	ND	ND
	Matanoski	2	1.7	1.2	ND	ND	ND
Industrial	Acheson	5	6.1	0.82	ND	ND	ND
	Liebling, Marsh[b]	7	3.1	2.3	ND	ND	ND
	Tabershaw	ND	ND	ND	ND	ND	ND
	Fayerweather	ND	ND	ND	ND	ND	ND
Brain	Walrath (New York)	9	5.8	1.6	3	1.8	1.7
Professional	Walrath (California)	9	4.7	1.9	7	2.7	2.6
	Stroup	10	3.7	2.7	6	1.7	3.5
	Levine	3	2.6	1.2	ND	ND	ND
	Harrington (Study No. 2)	4	1.2	3.3	ND	ND	ND
	Matanoski	5	4.6	1.1	ND	ND	ND
Industrial	Acheson	5	12.5	0.40	ND	ND	ND
	Liebling, Marsh	ND	ND	ND	ND	ND	ND
	Tabershaw	1	0.7	1.4	ND	ND	ND
	Fayerweather	ND	ND	ND	ND	ND	ND
All lymphatic and hemopoetic	Walrath (New York)	25	20.6	1.2	11	9.1	1.21
Professional	Walrath (California)	19	15.5	1.2	ND	ND	ND
	Stroup	18	14.6	1.2	ND	ND	ND
	Levine	8	6.5	1.2	ND	ND	ND
	Harrington (No. 1)	8	3.8	2.3	ND	ND	ND
	Harrington (No. 2)	2	3.0	0.7	ND	ND	ND
	Matanoski	ND	ND	ND	ND	ND	ND
Industrial	Acheson	20	26.3	0.8	ND	ND	ND
	Marsh	2	2.3	0.9	ND	ND	ND
	Tabershaw	3	2.0	1.5	ND	ND	ND
	Fayerweather	ND	ND	ND	1	0.95	1.00
Leukemia (only)	Walrath (New York)	12	8.5	1.4	ND	ND	ND
Professional	Walrath (California)	12	6.9	1.7	10	4.3	2.3
	Stroup	10	6.7	1.5	7	4.1	1.7
	Levine	4	2.5	1.6	ND	ND	ND
	Harrington (No. 1)	1	1.5	0.7	ND	ND	ND
	Harrington (No. 2)	1	1.1	0.91	ND	ND	ND
	Matanoski	ND	ND	ND	ND	ND	ND
Industrial	Acheson	9	11.4	0.8	ND	ND	ND
	Liebling, Marsh	ND	ND	ND	ND	ND	ND
	Tabershaw	ND	ND	ND	ND	ND	ND
	Fayerweather	ND	ND	ND	ND	ND	ND
Lung	Walrath (New York)	72	66.8	1.1	35	34.7	1.0
Professional	Walrath (California)	41	42.8	1.0	28	30.8	0.9
	Stroup	12	43.0	0.3	6	29.3	2.0
	Levine	19	20.2	0.94	19	18.4	1.0

Table 6. (continued)

Site	Study	No induction period considered			Induction period considered		
		O	E	O/E	O	E	O/E
	Harrington (No. 1)	10	27.4	0.4	ND	ND	ND
	Harrington (No.2)	9	22.0	0.41	ND	ND	ND
	Matanoski	12	21.4	0.6	ND	ND	ND
Industrial	Acheson	205	215.0	1.0	86	72.1	1.2
	Marsh	6	7.1	0.9	3	3.7	0.8
	Tabershaw	3	5.2	0.6	ND	ND	ND
	Fayerweather	ND	ND	ND	12	14.0	0.9
Prostate	Walrath (New York)	15	16.4	0.91	ND	ND	ND
Professional	Walrath (California)	23	13.1	1.8	16	9.5	1.7
	Stroup	20	18.7	1.1	ND	ND	ND
	Levine	3	3.4	0.88	ND	ND	ND
	Harrington (No. 1)	ND	ND	ND	ND	ND	ND
	Harrington (No. 2)	ND	ND	ND	ND	ND	ND
	Matanoski	ND	ND	ND	ND	ND	ND
Acheson	Acheson	ND	ND	ND	ND	ND	ND
	Liebling, Marsh	ND	ND	ND	ND	ND	ND
	Tabershaw	2	0.55	3.6	ND	ND	ND
	Fayerweather	ND	ND	ND	ND	ND	ND
Skin	Walrath (New York)	8	3.6	2.2	4	1.3	3.1
Professional	Walrath (California)	2	3.4	0.6	ND	ND	ND
	Stroup	2	3.5	0.6	ND	ND	ND
	Levine	0	0.9	0	ND	ND	ND
	Harrington (No. 1)	ND	ND	ND	ND	ND	ND
	Harrington (No.2)	ND	ND	ND	ND	ND	ND
	Matanoski	ND	ND	ND	ND	ND	ND
Industrial	Acheson	ND	ND	ND	ND	ND	ND
	Liebling, Marsh	ND	ND	ND	ND	ND	ND
	Tabershaw	0	0.4	0	ND	ND	ND
	Fayerweather	ND	ND	ND	ND	ND	ND
Bladder	Walrath (New York)	7	7.3	1.0	ND	ND	ND
Professional	Walrath (California)	8	5.8	1.4	ND	ND	ND
	Stroup	5	7.2	0.7	ND	ND	ND
	Levine	ND	ND	ND	ND	ND	ND
	Harrington (No. 1)	1	2.1	0.5	ND	ND	ND
	Harrington (No. 2)	2	1.9	1.1	ND	ND	ND
	Matanoski	ND	ND	ND	ND	ND	ND
Industrial	Acheson	ND	ND	ND	ND	ND	ND
	Marsh	1	0.3	3.3	ND	ND	ND
	Tabershaw	ND	ND	ND	ND	ND	ND
	Fayerweather	ND	ND	ND	3	0.6	5.3
Kidney	Walrath (New York)	8	5.4	1.5	2	2.4	0.83
Professional	Walrath (California)	4	4.0	1.0	ND	ND	ND
	Stroup	1	4.0	0.25	ND	ND	ND
	Levine	1	1.7	0.6	ND	ND	ND
	Harrington (No. 1)	ND	ND	ND	ND	ND	ND
	Harrington (No. 2)	ND	ND	ND	ND	ND	ND
	Matanoski	7	3.6	1.9	ND	ND	ND
Industrial	Acheson	ND	ND	ND	ND	ND	ND
	Liebling, Marsh	ND	ND	ND	ND	ND	ND
	Tabershaw	1	0.4	2.5	ND	ND	ND
	Fayerweather	ND	ND	ND	ND	ND	ND
Digestive system	Walrath (New York)	68	65.2	1.0	ND	ND	ND
Professional	Walrath (California)[c]	68	55.7	1.2	33	25.4	1.3
	Stroup	38	66.4	0.6	ND	ND	ND
	Levine	17	22.6	0.8	ND	ND	ND
	Harrington (No. 1)	12	19.8	0.6	ND	ND	ND
	Harrington (No. 2)	8	15.5	0.5	ND	ND	ND
	Matanoski	ND	ND	ND	ND	ND	ND

Table 6 (continued)

Site	Study	No induction period considered			Induction period considered		
		O	E	O/E	O	E	O/E
Digestive system	Acheson	ND	ND	ND	ND	ND	ND
Industrial	Marsh[c]	8	6.3	1.3	ND	ND	ND
	Tabershaw	0	4.1	0.0	ND	ND	ND
	Fayerweather[d]	ND	ND	ND	6	7.5	0.8

[a]Data from: Acheson (*55*); Fayerweather (*56*); Harrington or Harrington (No. 1) (*57*); Harrington (No. 2) (*58*); Levine (*59*); Matanoski (*60*); Stroup (*61*); Walrath (New York) (*62*); Walrath (California) (*63*); Liebling (*66*); March (*64*); Tabershaw (*65*). ND = no data.
[b]Including two "post closing" deaths.
[c]Stomach, colon and pancreas.
[d]Colon and rectum.

Table 7. Observed and expected deaths for professionals and industrial workers exposed to formaldehyde, with exact 95% confidence limits (CL).

Site of cancer	Professional		Industrial		Total	
	Obs/Exp	CL	Obs/Exp	CL	Obs/Exp	CL
Nasal	0/1.7	0–2.17	0/1.3	0–2.84	0/3.0	0–1.23
Mouth	20/23.8	0.51–1.30	12/9.2	0.67–2.28	32/33.0	0.66–1.37
Brain	40/22.6	1.26–2.41	6/13.2	0.17–0.99	46/35.8	0.94–1.71
Lymphatic and hematopoietic	80/64.0	0.98–1.53	25/30.6	0.53–1.21	105/94.6	0.91–1.34
Leukemia	40/27.2	1.05–2.00	9/11.4	0.36–1.50	49/38.6	0.94–1.68
Other lymphatic and hematopoietic	40/36.8	0.78–1.48	16/19.2	0.48–1.35	56/56.0	0.76–1.30
Lung	175/243.6	0.62–0.83	214/227.3	0.82–1.08	389/470.9	0.75–0.91
Prostate	61/51.6	0.90–1.52	2/0.6	0.40–12.04	63/52.2	93–1.54
Skin	12/11.4	0.54–1.84	0/0.4	0–9.22	12/11.8	0.52–1.78
Bladder	23/24.3	0.60–1.42	1/0.3	0.18–18.6	24/24.6	0.62–1.45
Kidney	21/18.6	0.70–1.73	1/0.4	0.06–13.93	22/19.0	0.72–1.75
Digestive System	211/245.2	0.74–0.98	8/10.4	0.33–1.52	219/255.6	0.75–0.98
Other causes						
Cirrhosis of liver	83/59.3	1.11–1.74	10/9	0.53–2.04	93/68.3	1.10–1.67
Nonneoplastic respiratory disease	109/163.7	0.55–0.80	243/241.1	0.88–1.14	352/404.8	0.78–0.96

of the brain is noted among the professional workers exposed to formaldehyde (40 obs, 22.6 exp; 95% CL for the SMR 126–241) (*58–63*). Among industrial workers, on the other hand, there is a substantial deficit (6 obs, 13.2 exp; 95% CL for the SMR 17–99) (*55,70*). The latter result, however, is derived from only two studies of which one contributes five observed cases and 12.5 expected. An excess of an approximately similar order of magnitude is seen in each of the three professional groups, namely embalmers, anatomists and pathologists, and within each of three separate groups of embalmers; the SMR increased when induction period was taken into consideration (see Table 6) (*55, 70*). Among anatomists 10 cases were observed and 3.7 expected; all the tumors were glioblastomas or astrocytomas. Among pathologists, all four brain cancers were of the glioma or astrocytoma cell type. Data from some autopsy series indicate that about 30% to 50% of primary intracranial neoplasms are of these cell types. Brain cancer is difficult to diagnose and may be more effectively detected among persons with better access to sophisticated medical care, particularly among groups such as medical faculty members (*71*). In discussing his study of medical professionals, Harrington (*58*) remarked that, " . . . social class gradients are relatively unimportant in this tumor . . . , and there is no excess in medical practitioners as a group." When the expected numbers in the study of anatomists (*61*) were based on either the mortality experience of psychiatrists, or based on the records of Olmsted County, in which the Mayo Clinic is located, the excess brain cancer mortality remained. Olmsted County has a very high autopsy rate, and brain cancer mortality is not likely to have been seriously underestimated. Thus, detection bias would not seem to account for the excessive brain cancer risk among anatomists.

The association between professional groups engaged in preservation of human tissues and brain cancer does not necessarily implicate formaldehyde. Aside from formaldehyde and human tissues themselves, however, it is unclear what other important occupational exposures these professional groups shared. The British study, which shows a deficiency of brain tumors among industrial workers (*55*), provides evidence against an association, although professional and industrial workers studied have differed in level, duration and frequency of exposure to both formaldehyde and other substances, chemical and biological.

Lymphatic and Hemopoietic System. When taken as a single group, no significant excess of deaths from these cancers was observed (105 obs, 94.6 exp; 95% CL for the SMR 91–134) (*55,57–59,61–63,70*). However, an excess exists that approaches significance for professional workers (80 obs, 64 exp; 95% CL for the SMR 98–156). This excess is primarily attributable to an excess of deaths from leukemia in this group (40 obs,

27.2 exp; CL for the SMR 105–200), particularly among those with an induction time of 15 years or more (17 obs, 8.4 exp; 95% CL for the SMR 118–324). In the past leukemia has been reported more frequently in the higher social classes. Among the anatomists (*61*), an excess of leukemia deaths, in particular, deaths due to chronic myeloid leukemia, persisted when compared with the mortality experience of psychiatrists. Thus, detection bias would not seem to account for the excessive leukemia risk among anatomists. The number of cases of leukemia reported among industrial groups exposed to formaldehyde is approximately as expected. Remarks about exposures and working practices of the various groups made in the previous paragraph also apply here.

LUNG. A deficiency of deaths from cancer of the lung is noted which is statistically significant among the professional workers (175 obs, 243.6 exp; 95% CL for the SMR 62–83) (*57–63*) and both groups combined (389 obs, 470.9 exp; 95% CL for the SMR 75–91), but not among the industrial workers (214 obs, 227.3 exp; 95% CL for the SMR 82–108) (*55,64,70*). The most likely explanation for the deficiencies is that exposed professional workers have been compared with a reference population that has smoked more; data on smoking habits are not available in any of these studies. In the British study (*55*), a significant increase in mortality from lung cancer was found in one of the six factories studied (British Industrial Plastics) (SMR = 124, 95% CL 104–148) in comparison with an expected number calculated from national death rates. This factory contributed over half of the lung cancer deaths and also had the highest average exposures; a trend of increasing mortality (as measured by the SMR) with increasing exposure to formaldehyde was found in the same factory and its significance was borderline at the 5% level. No such relation was found in any of the other factories or when all six factories were considered together. The number of men, however, exposed to "medium" or "high" levels of formaldehyde in the other factories was small. No relation was found between lung cancer mortality and exposure to formaldehyde as measured by length of service. Similarly, no relation was found between lung cancer mortality and interval since first exposure to formaldehyde. Men who entered the BIP factory between 1936 and 1945 (when exposure levels were probably highest) had the highest mortality from lung cancer. As the data now stand, there is some evidence of a dose-response relation between exposure to formaldehyde and lung cancer; the evidence derives from the one British factory where the largest number of cohort members experienced the highest formaldehyde exposure levels.* If formaldehyde is a human carcinogen, it might only be detectable through study of populations who experience high exposure levels, given the steep dose response exhibited by experimental animals.

In individual studies, attention has been drawn to small excesses of deaths from cancer of the prostate, skin (including melanoma), kidney, bladder, and of the digestive system. As can be seen from Table 7, in none of these sites, with the possible exception of prostate cancer, do the figures approach statistical significance in either professionals or industrial workers. There is at present scant evidence of an association between exposure and cancer of any of these sites.

Results from the DuPont case-control (*56*) study were evaluated and compared with findings from SMR and proportionate morbidity ratio (PMR) studies. Exposure to formaldehyde for the 481 cancer deaths and 481 living controls was estimated from work histories. Approximately 20% of both the control series and the cases were exposed to formaldehyde. The authors adjusted for age, sex, pay class, plant site and smoking history but presented crude odds ratios having found that adjustment made little difference. Numbers of many cancers were insufficient for meaningful analysis. No nasal cancers were reported. Among the seven cancers of the buccal cavity and seven melanomas of the skin, only one case of each was exposed to formaldehyde. Odds ratios were not elevated substantially for cancers of the brain, kidney, lung, or lymphatic and hematopoietic system. Risk gradients were noted for cancer of the prostate and bladder by cumulative exposure index (CEI). Compared with a value of 1.0 among nonexposed, odds ratios were 3.0 for CEI $\leq$ 20 and 3.6 for CEI $>$ 20 for cancer of the prostate. For bladder cancer, the odds ratios were 2.6 for CEI $\leq$ 20 and 5.2 for CEI $>$ 20. A case-control study of lung cancer in Danish doctors could not be evaluated because of an error in the analysis (*74*).

The data are sparse and conflicting and do not yet provide persuasive evidence of a causal relation between exposure to formaldehyde and cancer in man. As far as nasal cancer is concerned, the evidence is against a substantial (e.g., 10-fold) immediate increase in risk, but sufficient information is not yet available to exclude such an effect if risk starts to increase 20 years or more after first exposure. An increase in risk of brain cancer and leukemia is noted among each of three professional groups who preserve human tissues with solutions containing formaldehyde and other chemicals.

In view of the small numbers of person-years of follow-up in subjects followed for 20 years or more and various methodological limitations of the studies, it is not possible from the available epidemiological data to exclude the possibility that formaldehyde is a human carcinogen.

1e. Although on general grounds there is reason to believe that there is a wide variation in the susceptibility of individuals to carcinogens there is insufficient evidence to date by which to identify any particular subgroup as having greater than average susceptibility to a putative carcinogenic action of formaldehyde.

* Dr. Acheson, who could not attend the second meeting of the panel in Boston, suggested, based upon follow-up data, from studies he conducted which were not available at the time of the second meeting (*72,73*), that this sentence be replaced with "There is evidence within this factory of a relation between degree of exposure to formaldehyde and lung cancer, but the trend disappears when account is taken of length of exposure."

1d. Formaldehyde and Other Conditions. MORTALITY. No excess mortality from disease of the respiratory system (other than cancer) as a whole has been noted although lack of information on smoking severely limits interpretation. No detailed examination of mortality from particular respiratory diseases has been undertaken (Table 7). A statistically significant excess mortality from cirrhosis of the liver has been observed in the professional groups (83 obs 59.3 exp; 95% CL for the SMR 111–174) (*57–59,62,63*). No such excess was found in industrial workers (10 obs, 9.0 exp; 95% CL for the SMR 53–204), but these figures were derived from one study (*55*). The possibility of an excess consumption of alcohol should be considered as a possible explanation for the excess among embalmers, although there is no direct evidence to support this conjecture.

MORBIDITY The panel summarized studies measuring primarily symptoms and/or changes in pulmonary function (*74–82*). Symptoms (particularly irritation of the eyes, nose and throat) were consistently reported more frequently in the exposed populations, and were reported even when there were no reductions in pulmonary function. No important reductions in forced vital capacity were observed. Reductions in forced expiratory volume in one second (FEV) and forced expiratory volume % (FEV/FVC) when observed were small. These were not detected when exposure to formaldehyde was solely as a vapor. There was either a weak or absent association of reduced pulmonary function test with exposure in the few studies where this factor was analyzed. Workshift (acute) changes in pulmonary function test (PFT) have been assessed only when other dust was present and/or the formaldehyde itself was a particulate or incorporated in particles. Acute PFT reductions were not consistently present, were small and showed no regular association with exposure. Although some symptoms were present, the changes in PFT were clinically insignificant, and there is no convincing evidence formaldehyde exposure results in restriction or obstruction at the doses studied. There is some suggestion that the symptoms are reversible and of minor import. However, because of the demonstrated irritant potential of formaldehyde, selection bias may be occurring in the exposed populations so that these studies are likely to underestimate adverse effects of formaldehyde exposure.

Topic 2. Future Studies

Further case-control and cohort mortality studies are needed, both of industrial and professional workers exposed to formaldehyde and of persons exposed to formaldehyde in mobile and other homes. These studies should include estimates of the degree of exposure to formaldehyde and other chemicals; the analyses should take into account various possible induction times for a formaldehyde effect, as well as possible confounding by smoking habits and alcohol consumption. The possibility that there may be an inverse relation between degree of exposure to formaldehyde and smoking habits should be examined.

The panel wished to draw particular attention to the consistent excesses of malignant brain tumors (and leukemia) reported in several groups of professionals who use formaldehyde in the preservation of human tissues. Studies should be undertaken to measure the patterns of exposure to formaldehyde in these occupations, and to identify other chemical and biological exposures.

Longitudinal studies of the effects (if any) of exposure to formaldehyde gas and particulates on pulmonary function are needed as the data currently available are derived from cross-sectional studies.

Carcinogenicity/Histopathology/ Genotoxicity Panel Report*

Topic 1. What conclusions can be drawn from the available experimental data relative to the carcinogenicity/genotoxicity of formaldehyde? Are there data from studies that permit projections to be made about potential human responses?

a. What role does the cytotoxicity of formaldehyde play in its carcinogenicity in experimental animals?
b. What is the significance of benign tumors and potential preneoplastic lesions in the carcinogenic response in rats exposed to formaldehyde by inhalation?
c. What do genotoxicity studies tell us about the potential of formaldehyde to be an initiator or promoter for carcinogenesis or a mutagen in somatic or germ cells?
d. What nonneoplastic changes occur when experimental animals and man are exposed to formaldehyde? What is the health significance of these changes?

Topic 2. What critical questions remain to be answered?

Topic 1: Conclusions from Experimental Data

1. Data on the carcinogenicity of formaldehyde vapor are available for the rat, mouse, and hamster. Carcinogenicity for the nasal epithelium has been demonstrated in two strains of rats exposed by inhalation for 6 hr/day, 5 days/week, for up to 2 years, to concentrations of approximately 14 ppm formaldehyde (*83,84.*† The same exposure regimen in one experiment, but at a concentration of 5.6 ppm, produced a greatly reduced incidence of nasal cancer, 2 out of a total

* Carcinogenicity/Histopathology/Genotoxicity Panel: Richard Griesemer (Chairman); Craig Boreiko; Frederick J. de Serres; Victor J. Feron; J. Justin McCormick; James A. Swenberg; Benjamin F. Trump; A. Upton; J. Ward.

† The number of rats with nasal carcinoma at concentrations of 14.3 ppm was an adjusted incidence of 103 out of 206.

of 235 rats of both sexes (*83*). About 80% of both sexes at this dose level survived 2 years and, therefore, were at risk to late developing lesions. No nasal tumors, other than polypoid adenomas, were found in the same experiment in rats exposed to concentrations of 2 ppm.

For mice, only one adequate study has been reported in which 2 out of a total of 215 mice exposed to a concentration of 14 ppm developed nasal cancers after 24 months of exposure (*83*). Although not statistically significant in comparison with matched control mice, the finding is considered strongly suggestive in comparison to historic control mice in which nasal cancers are rare. The difference in susceptibility of rats and mice might be attributed to greater reductions in respiratory minute volume in mice than rats during exposure to the irritant vapor (*85*).

Eighty-eight male Syrian hamsters exposed to 10 ppm formaldehyde vapor, 5 hr/day, 5 days/week for their lifetime had no detected respiratory cancers (*86*). However, only two microscopic sections of the nose were examined for each animal. In another experiment by the same group of investigators, male hamsters exposed to 30 ppm formaldehyde for 5 hr a day, once a week for lifetime also had no tumors observed in the respiratory tract. When male hamsters received a 5-hr exposure to 30 ppm formaldehyde 2 days prior to each of 10 weekly injections of diethylnitrosamine (DEN), the average number of tracheal tumors per tumor-bearing animal was reported to be increased as compared with those hamsters receiving DEN alone. Inspection of the data presented in the report, however, showed a corresponding decrease in lung tumors in hamsters exposed to both agents, suggesting that the effect on the trachea may be within the limits of experimental variability. The reported cocarcinogenicity requires confirmation.

The available data indicate that hamsters are much less susceptible to the carcinogenic effects of formaldehyde than rats and that mice are intermediate in response. It should be emphasized, however, that the data available for species comparisons are limited to very few experiments. It may be relevant that acetaldehyde, a structurally related compound, is carcinogenic for the nose and larynx of Syrian hamsters (*87*) and for the nasal passages of rats (*88*).

No compound-related skin cancers were found in any of the inhalation bioassays.

Several studies on the pathogenesis of formaldehyde-induced nasal cancer have been completed (*89*). Data from these are included in this panel's report as well as the report of the Structure Activity/Biochemistry/Metabolism Panel. Collectively, these suggest that the toxic effects of formaldehyde are proportionately greater at high concentrations (i.e., 6–15 ppm) than at lower concentrations (i.e. < 2 ppm). For example, increasing the exposure concentration of formaldehyde from 6 to 14 ppm, less than a 3-fold increase, resulted in a 50-fold increase in squamous cell carcinomas in rats. Possible mechanisms for this include impairment of mucociliary clearance, detoxification, and DNA repair leading to greater effective target site doses. This panel considers differences in ambient air concentrations versus dose to target sites to be a likely explanation for the apparent nonlinearity in concentration response.

1a. Rodents exposed to formaldehyde by inhalation showed clear indications of cell damage in the nasal turbinates at concentrations that induced squamous cell carcinomas (*90*). The cytotoxic response was characterized by cell death, restorative cell proliferation and hyperplasia, and occurred in the same regions of the nasal passages that developed squamous cell carcinomas. This resulted in alteration of the nasal epithelium from a tissue with low cell replications (i.e., 0.1–0.5% of the cells) to one with increased cell replication in the early time points sampled. Concentration has been shown to play a greater role than the concentration-time product in both acute studies and following exposure of rats for up to six months. No squamous cell carcinomas were observed at concentrations inducing less cytotoxicity.

The implications of these findings are that cytotoxicity might influence both initiation and promotion. If more cells of the target tissue replicate, there is a greater availability of single-stranded DNA for adduct formation, decreased time for repair of DNA adducts, and a greater chance of fixation of mutagenic events. Increased cell proliferation also contributes to tumor promotion. Thus, there is a greater likelihood of tumor development with the increased cell proliferation associated with cytotoxic exposures. Other chemicals classified as tumor promoters (i.e., nitrilotriacetic acid, phenobarbital, saccharin and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin) also induce tumors primarily at doses which result in cytotoxicity and chronic hyperplasia in target organs. These factors are likely to contribute to the nonlinearity of the dose response, i.e., proportionately greater response at higher doses.

1b. Benign Tumors. Carcinogens induce both benign and malignant tumors. Carcinogens which induce benign tumors almost always induce malignant tumors in the same experiment or other experiments. Benign tumors in rodents may progress to malignant tumors. It is impossible to predict whether or not a specific benign tumor will progress to a malignant tumor.

In the case of formaldehyde (*83*), a high incidence of malignant tumors (squamous cell carcinomas) was induced in rats exposed to 14 ppm formaldehyde gas. Papillomas, which the panel believes represent the benign counterpart of the squamous cell carcinoma, were not observed. A second type of benign lesion, polypoid adenoma, occurred in all exposure groups and one control animal. Six of the 20 lesions originally diagnosed as polypoid adenomas in the study conducted at the Chemical Industry Institute of Toxicology (CIIT) (*83*) were reviewed by pathologists on the panel and in the audience. They considered the lesions to represent a mixture of polypoid adenomas, nonneoplastic polyps and hyperplasias. (Subsequent independent review of the lesions originally diagnosed as polypoid adenomas in the CIIT study essentially confirmed the presence of

polypoid adenomas in the study, although a few lesions were considered to be borderline between adenoma and hyperplasia.) The panel recommends that this group of lesions not be combined with squamous cell carcinomas for risk estimation because of the differences in the cell type of origin. The polypoid adenomas can be evaluated separately and in combination with the nonsquamous carcinomas that were observed in the 14 ppm rats.

1b. Potential Preneoplastic Lesions. Preneoplastic lesions may be induced by carcinogens. The morphologic, histochemical and biologic properties of these lesions are best studied by serial sacrifice experiments and reversibility studies. In these types of studies, specific lesions may be characterized and a sequence of the histopathogenesis of cancer postulated. Some information of this type is available for formaldehyde. Based on incidence in serial sacrifice studies, epithelial dysplasia and squamous metaplasia in rats and mice exposed to formaldehyde appear to regress after stopping the carcinogen exposure. It is uncertain if these reversible lesions are potentially preneoplastic, but their reversibility suggests that they are not committed to progress. More severe and typical lesions occurred only in the highest dose groups where tumors occurred. Adequate data are not available to draw any conclusions on regression or progression of the latter potentially preneoplastic lesions in the formaldehyde bioassay.

1c. The 1977 review of Auerbach et al. of the literature on the biological effects of formaldehyde (*91*) indicated that the ability of formaldehyde to cause genetic alterations in Drosophila larvae, fungi, and bacteria was known as early as the 1940s. Since 1977, new studies have demonstrated that formaldehyde can induce single-strand breaks in DNA (*92–94*), DNA–protein crosslinks (*92–96*), sister chromatid exchanges (*97,98*), and chromosome aberrations (*99*). It has also been shown to induce mutations in bacteria (*100–102*), yeast (*103–105*), Drosophila (*106*), mammalian cells (*97,107*) and human cells (*108*). *In vitro* evidence of formaldehyde's carcinogenic potential is provided by its ability to transform BALB/c 3T3 mouse cells (*97*), BHK 21 hamster cells (*107*) and C2H-10T1/2 mouse cells (*100,109*) to enhance the transformation of Syrian hamster embryo cells by SA7 adenovirus (*110*), and to inhibit DNA repair (*111*).

In reviewing the above literature, we have found that the recent work is more likely to find formaldehyde a mutagen than earlier studies and is also more likely to show a dose-response relationship. These results are most probably attributable to the greater sophistication in the way the later assays were carried out. It should be noted that in the above studies, the relationship between cytotoxicity induced by formaldehyde and mutagenicity (*108*) or transformation (*100,107,109*) induced by this agent is typical of most mutagens/carcinogens that are positive in these assays. The data we have reviewed are consistent with formaldehyde acting as a weak mutagen (i.e., less than a 10-fold increase over background).

Various studies have been undertaken to determine whether formaldehyde has a genotoxic effect *in vivo*. In mice, the dominant lethal test was found to be negative (*112*). However, in a more recent dominant lethal assay using higher doses and a different mouse strain, marginally positive results were obtained, but only in the first and third week of the seven weeks studied (*113*). Negative results were obtained when the induction of micronuclei (*114* or chromosomal aberrations (*97,113*) were used as an endpoint.

A small increase in sister chromatid exchanges has been reported in the bone marrow of mice exposed to high (> 25 ppm) formaldehyde concentrations. Unfortunately, technical problems were encountered during the formaldehyde exposures and the actual concentrations required to elicit this effect are not known (*95,115*).

The observation that formaldehyde is both genotoxic and carcinogenic suggests that *in vivo* exposures cause irreversible genetic alterations causally related to the acquisition of malignancy. *In vitro* studies suggest, however, that the genotoxic properties of formaldehyde are relatively weak. One can thus question whether promotional influences play a major role in the etiology of formaldehyde-induced neoplasms. Studies conducted to date suggest that formaldehyde possesses only weak activity for the promotion of transformation in cultures of C3H/10T1/2 cells (*116*) and similar weak promoting activity on mouse skin (*117*; Ward, personal communication). A second study on mouse skin failed to detect promotion following the application of nonirritating doses of formaldehyde (*118*). In addition, the exposure of DEN-treated hamsters to 30 ppm formaldehyde (*86*) was reported to increase the incidence of DEN-induced tracheal adenomas. Promoters exhibit marked tissue and species specificity and the possibility that formaldehyde might possess strong tumor-promoting properties in the rat nasal cavity cannot be excluded. Treatment with carcinogenic concentrations of formaldehyde induces extensive cell proliferation, a phenomenon reported to be sufficient for the promotion of tumorigenesis on mouse skin (*119,120*).

Most importantly, perhaps, the mouse spot test is reported to be negative in two separate studies (*115,120*), although the full data were not available to the panel. In one of these studies (*115*), difficulties were encountered in regulating the levels of formaldehyde exposure and levels in excess of 25 ppm probably occurred. Furthermore, while genotoxic effects were not observed in this study, there was some suggestion of embryotoxicity as evidenced by the production of white midventral spots. Still, since this assay is considered a good assessment of the ability of an agent to cause systemic effects, these negative results suggest that germ-cell assays would also be negative. Thus, there may not be a need for additional studies such as the specific locus test and the heritable translocation test.

1d. There is no convincing evidence in experimental animals that inhalation exposure causes significant

primary toxicologic effects in organs other than the upper respiratory tract.

Topic 2. Future Studies

Formaldehyde–DNA adducts have recently been partially characterized. Also, formaldehyde-induced DNA–protein crosslinks are reported to exist (Structure Activity/Biochemistry/Metabolism Panel). However, the biological relevance of these formaldehyde-induced DNA lesions has not been ascertained. Future studies should determine whether such adducts preferentially form on single stranded DNA within cells, what repair mechanisms remove such lesions, and whether the DNA lesions are associated with the cytotoxic, mutagenic, and transforming activity of formaldehyde.

Comparative molecular dosimetry studies following formaldehyde inhalation exposure are urgently needed to evaluate the relationship between exposure and dose to target site.

Additional carcinogenicity studies in rats at doses above, below, and between 2 and 14 ppm would be beneficial in better defining the dose-response curve.

Since rodents are obligate nose breathers, comparative toxicity/carcinogenicity studies in primates which have oronasal breathing patterns similar to man would be useful to further validate dosimetry studies as a means of carcinogenic risk assessment.

An animal model for initiation/promotion in the nasal epithelium should be developed.

Since formaldehyde and acetaldehyde are nasal carcinogens, information should be collected on structure-activity relationships of other aldehydes.

Summary

Formaldehyde gas is carcinogenic for rats and probably for mice, producing nasal tumors after inhalation. Limited experiments in Syrian hamsters have not demonstrated carcinogenicity. In rats, the carcinogenic response appears nonlinear, being disproportionately higher at the higher concentrations (14 ppm).

Cell killing and the reparative process that occurred in the inhalation bioassays may contribute to carcinogenicity, but the specific role of cytotoxicity in formaldehyde carcinogenicity is unknown. Cytotoxicity is not unique to formaldehyde bioassays and may play a role in the carcinogenicity of other chemicals as well.

A sample of the benign lesions observed in the Chemical Industry Institute of Toxicology (CIIT) study, originally diagnosed as polypoid adenomas, was reviewed by the panel and was considered to be a mixture of polypoid adenomas, nonneoplastic polyps and hyperplasias. Uncertainties about the nature of the remaining lesions in the study made the lesion unsuitable for use in risk assessment. Subsequent to the Consensus Workshop, an independent review essentially confirmed the original diagnoses in the CIIT study, indicating that they were then suitable for use in risk assessment, either separately (from squamous carcinomas), or in combination with nonsquamous carcinomas.

Formaldehyde is genotoxic in a number of assays and is weakly mutagenic in human cells in culture as well as in other mammalian cells, Drosophila, fungi and bacteria. Formaldehyde is a weak promoter in cell culture and on mouse skin. *In vivo* studies in mice are, in the main, negative, but marginally positive results have sometimes been seen at very high doses.

There is no convincing experimental evidence that formaldehyde has primary toxic effects at body sites distant from the site of exposure.

Immunology/Sensitization/ Irritation Panel Report*

Topic 1. What is the significance of reports that formaldehyde causes irritation and/or sensitization following topical or inhalation exposure?

a. Is formaldehyde a primary sensitizing agent or does it elicit a response only in presensitized populations?
b. If irritation, primary or secondary sensitization occurs, who are the susceptible populations?
c. What are the possible mechanisms for formaldehyde-induced irritation/sensitization?
d. Do threshold levels exist for irritation/sensitization? If so, what are the levels and the concentration ranges? Do thresholds differ for different populations (sensitized)?
e. Is there evidence for effects of formaldehyde on the immune system?

Topic 2. What experiments would be most important to resolve any controversies in this area?

Topic 1. Significance of Sensitization Reports

Any assessment of reports on irritation by and/or sensitization to formaldehyde requires some definition of terms. Allergy can be defined as the acquired, specific, altered capacity to react. The general criteria suggestive of this are: a period of exposure to nonirritant or irritant concentrations, i.e., the period of sensitization; the elicitation of reactions by small amounts, far below those capable of inducing sensitivity or irritant effects. This is a distinguishing feature between irritation and sensitization. Last, only a few exposed subjects are likely to be sensitized. This is in contrast to irritant effects which are likely to occur in most subjects who are more heavily exposed to irritant concentrations. Demonstration of relevant, appropriate, humoral antibodies or sensitized lymphocytes provides strong evidence that the reaction is allergic.

Four different types of allergy can be induced.

* Immunology/Sensitization/Irritation Panel: Jack Pepys (Chairman); Paul Nettesheim (Alternate Chairman/Secretary); Yves Alaire; James R. Beall; Jack H. Dean; K. C. Gupta; Michael D. Lebowitz; Howard Maibach; Roy Patterson.

Type I. Immediate, anaphylactic reactions, coming on in minutes, are maximal in about 10 to 15 min and last about 1 to 1.5 hr. These reactions are mediated by IgE antibody, mainly in atopics, but also by IgG (short-term sensitizing) antibody. "Atopy" is defined here as the production of specific IgE to one or more common allergens with or without symptoms, a feature found in many studies in about 40% of individuals tested.

Type II. The antigens are altered body constituents, and where chemical haptens are involved, the antibodies are directed against the hapten-carrier complex.

Type III. Immune-complex complement-dependent allergy is mediated by precipitating antibodies. The reactions come on after several hours, are maximal at about 5 to 8 hr and resolve in about 24 hr. They are preceded in skin tests by an immediate, Type I introductory reaction.

Type IV. Delayed-type allergy is mediated by sensitized T-lymphocytes. It is the allergy of contact dermatitis and develops after about 24 hr, being maximal at about 48 to 96 hr and resolves slowly. The different types of allergy may be present together.

Studies with reactive low molecular weight chemicals have shown the participation of Types I and III allergy in allergic respiratory diseases such as rhinitis, asthma, etc. (*121,122*). Asthma is defined here as bronchial hyperactivity to specific immunological or nonspecific, nonimmunological factors. These can have effects one upon the other in clinical circumstances. Clinical observations and controlled bronchial provocation tests have shown a heterogeneity of patterns of asthmatic reactions. These can be immediate or nonimmediate. The immediate reactions have features of Type I, IgE and IgG (STS) reactions.

Nonimmediate asthmatic reactions have three forms. One comes on after 1 hr, is maximal at about 2 to 3 hr, and resolves in 5 hr. The next, and most common, comes on after several hours, is maximal at about 5 to 8 hr and resolves by 16 hr. Then there is the nocturnal reaction, coming on in the early hours of the morning and capable of recurrence at the same time each night for many nights, following a single challenge exposure as reported by Hendrick and Lane (*123*) in nurses using formalin for disinfection in a dialysis unit. The different patterns of asthmatic reaction may be present together. There is no evidence, however, that these patterns are necessarily due to the types of allergy they may resemble.

1. There are numerous reports that formaldehyde vapor exposure causes direct irritation of both the skin and respiratory tract (*36,38,124–144*). By comparison the evidence for allergic airway responses to formaldehyde is less extensive (*75,121,126,131,136,138,145–159*). Sufficiently well-controlled scientific studies are not available to definitively establish the development of respiratory tract allergy to formaldehyde gas *per se*. There are a few clinical reports in which tests were made for respiratory sensitivity to either formaldehyde gas or formaldehyde products, or both, and in which allergic reactions were elicited (*123,152,160–165*). The interpretation of the findings is uncertain since questions about the nature of the materials, the methods of testing and the statistical analysis of the data remain unanswered.

1a. Formaldehyde is definitely a primary skin sensitizing agent inducing allergic contact dermatitis (Type IV allergy) and probably immunologic contact urticaria (probably Type I allergy) (*38,75,121,135,136,145,149, 154,155,166–170*).

There is extensive experience suggesting that human beings with allergic contact dermatitis to one chemical are, in some situations, more likely to develop allergic contact dermatitis to another. On the other hand, other situations exist in which sensitization to one chemical iterferes with sensitization to a second. This panel is not aware of any controlled study that documents the ability of any other chemical to influence the sensitization rate to formaldehyde.

It is not known whether populations already sensitized to chemicals other than formaldehyde are at greater risk for inhalant sensitization to formaldehyde or its products. Assessment of a role for presensitization in people exposed to formaldehyde needs study in terms of atopy.

1b. Irritation and allergic contact dermatitis to formaldehyde occur. Although there is extensive literature on the effects of age, sex, race, and other factors on the ability of chemicals to induce allergic contact sensitization and irritation, there is no specific information on these matters for formaldehyde.

With respect to inhalant sensitization to formaldehyde, it is not known whether there are susceptible groups in the population. Conceivably, asthmatics might be more sensitive to the irritant action of formaldehyde, triggering bronchial reactions (*38,75,121,127,136,153, 161,163*).

In chronic dialysis patients sensitization to formaldehyde has been reported resulting from its release into the bloodstream from equipment and tubing sterilized with formaldehyde (*171–175*).

1c. Cutaneous Exposure. Formaldehyde skin irritation is nonimmunologic; studies as to how its mechanism differs from other forms of cutaneous irritation are not available. Formaldehyde allergic contact dermatitis presumably requires conjugation with protein and is taken to be a classical type of delayed hypersensitivity. Formaldehyde-induced contact urticaria has been documented and is presumably a Type I allergy. Nonimmunologic contact urticaria which requires multiple applications on the same site has been documented (*144*). Information on mechanisms is lacking.

1c. Inhalation Exposure. Irritation and potential predisposition to infections are seen. Two types of irritation can be caused by formaldehyde: sensory; and inflammation (*175,176*).

Sensory. Receptors of eyes, nose and throat may be affected (*36,38,124,127,177–179*). Man and animals can

develop short-term tolerance (*31,125,130,180,181*). There is evidence in experimental animals that with repeated exposure increased responses are obtained (*130*).

It requires higher concentrations of formaldehyde in the air to stimulate bronchial receptors, since the water-soluble formaldehyde reacts with and is retained in the upper respiratory tract (*175*).

At even higher concentrations, receptors in the peripheral lung tissues (*175*), in the conducting airways and the alveoli, have been stimulated in animals (*131,177,182,183*). To achieve this, nasal catheters were used to bypass the upper airways. Stimulation of receptors in the peripheral lung might occur if small particulate material from urea, phenol or other formaldehyde products and pressed wood dusts were deposited in these regions of the lung followed by hydrolytic release of formaldehyde (*182,184*). Other chemical components would have to be excluded as possible causes before the effects could be attributed to released formaldehyde.

At least three mechanisms exist whereby low molecular weight chemicals may cause sensory irritation (*185*), i.e., nucleophilic addition, disulfide bond cleavage and physical interaction. In the case of formaldehyde, nucleophilic addition is probably the most important mechanism. The reactivity is directed for example toward SH or NH_2 groups in proteins. Formaldehyde reacts with SH and NH_2 groups in a reversible way. The interaction with SH is less reversible than that with NH_2 (*186*).

Inflammation (with Cellular and Tissue Damage). Experiments in animals show that cellular damage and inflammation is induced with increasing severity at concentrations of formaldehyde of 1 to 15 ppm. Exposure for several hours is required and is accompanied by impaired ciliary activity (*176,187*).

Earlier studies implicate formaldehyde as a potential factor predisposing particularly children to respiratory tract infections (*181,188–190*). Appropriate epidemiological and animal studies need to be designed using specific criteria for infection and better protocols of the type used to investigate other irritant gases, such as O_3, SO_2, and NO_2 (*177,191–193*).

1c. Systemic Sensitization. Sensitization arising from release of formaldehyde into the circulation during dialysis has been reported. This is associated with frequent eosinophilia and some severe hypersensitivity and asthmalike reactions (*194,195*). The presence of auto-anti-N-like antibodies reacting with formaldehyde conjugated red blood cells is evidence of Type II auto-allergy (*171–174,196–201*). The anaphylactic reactions are suggestive of Type I allergy.

1d. Cutaneous Exposure. Threshold levels have been reported for cutaneous irritation and allergic contact dermatitis in the guinea pig and man. For human skin, a single application of 1% formalin in water with occlusion will produce an irritant response in approximately 5% of the population (*144*). The threshold for open application has not been determined. The threshold level for the induction of allergic contact dermatitis in man has only been imprecisely determined as less than 5% formalin in water. The approximate thresholds for elicitation of allergic contact dermatitis in sensitized subjects to formaldehyde range from 30 ppm for patch testing to 60 ppm for actual use concentrations of formalin. Because of the small data base these values must be regarded with caution until further studies become available (*144*).

The threshold for induction of immunologic contact urticaria has not been determined. For the induction of repetitive nonimmunologic contact urticaria is under 1% formalin in water or less (*144*).

1d. Inhalation Exposure. Precise thresholds have not been established for the irritant effects of inhaled formaldehyde. However, within the range of 0.1 to 3 ppm, most people experience irritation of the eyes, nose, and throat (*78,79,124,125,127,130,153,179,181, 202–205*). Between 10 and 20 ppm, symptoms are severe, and it becomes difficult to take a normal breath (*206*). Lower airways and pulmonary effects are likely to occur between 5 and 30 ppm. Exposures between 50 and 100 ppm cause serious injury to the respiratory tract, such as pulmonary edema, inflammation, pneumonitis and pneumonia (*130,136*). Asthmalike symptoms have been elicited by irritant concentrations.

There is no information regarding threshold values for sensitization to formaldehyde as an inhalant allergen.

1e. Only two animal studies on the potential toxic effects of inhaled formaldehyde on the immune system have come to our attention (*207,208*). No impairment of immune functions was found except in one of the studies where lethal concentrations were used (*208*).

Topic 2. Future Studies.

Cutaneous. Future studies should include defining the operational criteria for scientific documentation of the diagnosis of allergic contact dermatitis in man; determining the amount of formaldehyde required to induce and elicit the following reactions in man: irritant dermatitis, allergic contact dermatitis, nonimmunologic contact urticaria and contact urticaria; ascertaining the cross reaction pattern in allergic contact dermatitis in animal and man to formaldehyde-related chemicals; utilizing the above information, ascertaining populations susceptible to irritation, allergic contact dermatitis and immunologic and nonimmunologic contact urticaria; determining the relationship in allergic contact dermatitis between the degree of patch test reactivity and intolerance to actual product use.

Inhalation. Controlled cohort epidemiological studies of exposed and unexposed persons with particular emphasis on the formulation and application of protocols should be conducted. The application of standardized procedures is recommended.

Clinical studies should use basic protocols for pulmonary function studies and for testing for specific and nonspecific sensitivity. Comparisons of gaseous and

particulate materials for provocation test purposes are needed. Prospective comprehensive surveillance studies correlated with formaldehyde exposure measurements should be made, with detailed criteria to document the health hazards.

Sulfur dioxide and O_3 exposure of animals has been shown to promote airway infection to bacterial and viral agents. Similar studies should be conducted with formaldehyde. Appropriate epidemiological studies with acceptable criteria for respiratory infection should be conducted to determine the effects of formaldehyde on respiratory infections in humans.

A larger data base should be established on sensory and irritant thresholds in normal subjects in all age groups including individuals with respiratory tract symptoms.

Laboratory studies need to be conducted to search for serological and cellular antibody activity in groups who are or appear to be sensitive to formaldehyde and in particular in the hemodialysis patient population in whom allergic sensitivity to formaldehyde has been reported. This may provide a basis for immunological studies of respiratory tract responses to formaldehyde.

Animal models need to be developed for observations of biological effects of differing formaldehyde exposures and for studies of the mechanisms of formaldehyde irritation and sensitization.

Chemical characterization of formaldehyde products is needed. The behavior of such products in the atmosphere and their biological effects and interrelationships need to be investigated.

Structure Activity/Biochemistry/Metabolism Panel Report*

Topic 1. What is known about the metabolism and fate of exogenous and endogenous formaldehyde in experimental animals and man?

a. What are the data concerning binding of formaldehyde or its metabolic products to cellular macromolecules?
b. Are there common biological effects induced by short-chain aldehydes that can be predicted on the basis of structure activity relationships?
c. What are the quantitative relationships between exposure levels and concentrations of formaldehyde in particular tissues and organs?
d. Are there compounds that exert an effect by forming formaldehyde during metabolism?

Topic 2. What future studies would resolve uncertainties in this area?

The Panel on Structure Activity/Biochemistry/Metabolism recognizes as a basic challenge the question of how a vitally important intermediate in the normal metabolism of cells, a compound which serves as a building-block for the synthesis of purines, pyrimidines, many amino acids and lipids, a key molecule in one-carbon metabolism which is present in normal tissues, can induce cancer in animals on inhalation.

Topic 1. Metabolism of Formaldehyde

1a. There is now a large and growing body of data which infers that formaldehyde, like many other chemical carcinogens, acts as an electrophile with macromolecules such as DNA, RNA and protein to form reversibly bound adducts or irreversible crosslinks and that the modifications in DNA caused thereby are relevant to the neoplastic transformation.

1b. Formaldehyde is not unique as a carcinogenic aldehyde, since other aldehydes, such as acetaldehyde, acrolein, malondialdehyde and glycidaldehyde are also carcinogenic. It is likely, though not certain, that all of these aldehydes have a common mode of action: through modification of DNA by formation of adducts or crosslinks. Differences in the degree and tissue targets of carcinogenesis are readily attributable to differences in activities and localizations of activating and/or competing enzyme systems, and to differences in physical properties, solubilities and partition between cell membranes.

1a. Supporting a role of DNA modification in formaldehyde toxicity is its clear-cut mutagenic activity. It is mutagenic in three strains of *Salmonella typhimurium* and initiates neoplastic transformations in $C_3H/10T1/2$ mouse fibroblasts when treated together with the tumor promoter, 12-O-tetradecanoyl phorbol 13-acetate (TPA). Formaldehyde at concentrations of 0.017 to 0.083 mM also caused transformation of BALB/c3T3 and baby hamster kidney cells and caused mutations in cultured human lymphoblasts at concentrations greater than 0.13 mM and chromosomal aberrations in diploid human fibroblasts at 2 to 8 mM.

Reactivity. Formaldehyde reacts virtually instantaneously with primary and secondary amines, thiols, hydroxyls, and amides to form methylol derivatives, which in some instances can lose water to form the corresponding Schiff bases. The thiols have a somewhat higher affinity for formaldehyde than amines and adducts with glutathione or beta-mercaptoethanol are quite stable.

Formaldehyde forms unstable adducts with DNA, RNA and proteins, but when crosslinked, these are far more stable. DNA–protein adducts have been demonstrated in several eukaryotic and prokaryotic cell types, and are formed at the same concentrations of formaldehyde that cause mutation and cell transformation.

Metabolism. Formaldehyde is normally formed endogenously, as the N^5,N^{10}-methylenetetrahydrofolic acid, which equilibrates rapidly with other tetrahydrofolate derivatives. The major sources are serine and glycine; however, other sources are *N*-methylamino acids, methio-

* Structure Activity/Biochemistry/Metabolism Panel: Sidney Weinhouse (Chairman); James E. Gibson (Alternate Chairman/Secretary); Joseph Arcos; Ruth E. Billings; Henry d'A. Heck; Thomas R. Tephly; Andrew G. Ulsamer; Phillip G. Watanabe. Background for the information in this report may be found in the data base in Appendix I to the Consensus Workshop document and in the references (*38,49, 141,143,186,209–211*).

nine and other methyl-containing substances, and all of these can be formed by the many reversible reactions involving tetrahydrofolate derivatives. Metabolic reactions involving tetrahydrofolic acid (THFA) derivatives allow formaldehyde carbon to enter virtually every metabolite in the cell.

The total concentration of formaldehyde, free and bound, in freshly collected livers of F-344 rats is 0.1 to 0.2 μmole/g fresh weight, very little of which is in the form of N^5,N^{10}-methylene THFA.

Oxidation. The major pathway of formaldehyde oxidation is to formic acid, for which three enzymatic pathways are known. By far the most important is catalyzed by formaldehyde dehydrogenase, which oxidizes the formaldehyde–glutathione adduct with NAD^+ to yield S-formylglutathione and NADH. The former is hydrolyzed to formate and glutathione by a hydrolase present in excess. The affinity of formaldehyde for formaldehyde dehydrogenase in respiratory and olfactory mucosa is 2.5 μM, which is in the range of normal formaldehyde concentration, whereas the nonspecific aldehyde dehydrogenase, has an affinity 200-fold lower; completely outside the range for physiological significance. Formaldehyde is also oxidized to formate by hydrogen peroxide, catalyzed by catalase, but the quantitative significance and sites of action are not known.

1c. Formaldehyde disappears from the plasma with a half-time of about 1 to 1.5 min. Removal is so rapid that an increase cannot be detected in the plasma of animals or humans immediately following inhalation exposure to high concentrations. In intact animals, a high percentage of the formaldehyde administered is converted to CO through formate with smaller amounts excreted in the urine as formate and several other minor metabolites.

Despite its rapid removal, the possibility exists that transient increases in formaldehyde may occur in the intact animal. The panel could not exclude the possibility that formaldehyde may be transported to, and exert toxic effects at, distant sites following inhalation, but definitive evidence for effects of formaldehyde *per se* at distant sites is lacking.

1d. Formaldehyde from Xenobiotics. Besides its formation from normal metabolites, formaldehyde is produced in the oxidative demethylation of drugs and other foreign substances by the microsomal cytochrome P-450 monooxygenases. Such endogenous formaldehyde may exert toxic effects; for example, hexamethylphosphoramide is a potent nasal carcinogen and a mutagen acting, presumably, by conversion of its methyl groups intracellularly to formaldehyde. Other substances that may be toxic by virtue of conversion to formaldehyde would be methanol and methyl chloride, but existing evidence for a toxic role of formaldehyde is to the contrary.

Significance of Nonlinear Carcinogenic Response to Formaldehyde Exposure. At 15 ppm, formaldehyde is an effective nasal carcinogen in the rat, but there are few tumors at 6 ppm. This non linear response to dosage, in contrast with the linear response of DNA–protein crosslinks at 6 ppm and above, suggests a role for nongenetic factors in formaldehyde carcinogenesis. However, it should be recognized that only certain specific sites on DNA might lead to carcinogenesis. Moreover, the rapid and nondiscriminate attack of formaldehyde on tissue components could involve membrane function, transport and repair processes, and it is known that mucociliary removal of formaldehyde is inhibited at high concentrations. In view of this complex network of reinforcing and competing reactions, it is not surprising that the carcinogenic response is not linear or that it does not parallel the degree of crosslinks. Although the cause is still uncertain, this apparent nonlinearity cannot be construed to indicate the existence of a threshold for exogenous formaldehyde carcinogenicity. Although nongenetic factors may play a role, more sensitive methods will be required to determine whether a linear relationship between dose and response exists at low exposure levels. The mutagenicity of formaldehyde in a variety of experimental systems and the formation of DNA adducts and cross links both *in vivo* and *in vitro* point to modification of DNA or in the repair of damaged DNA as critical steps in the induction of cancer by formaldehyde.

The exclusive formation of nasal tumors in animals exposed to formaldehyde does not signify any special susceptibility and can only be attributed to its location at the site of entry of gaseous formaldehyde.

The reason why endogenous formaldehyde, formed constantly during normal metabolism and occurring at low concentrations in body fluids, is apparently not harmful still remains a mystery. The mystery is compounded by the fact that exposure to formaldehyde does not lead to any appreciable rise in body fluid levels. More information is required on the metabolism and pharmacokinetics of exogenous formaldehyde. Although there are differences in formaldehyde carcinogenicity among different species, at present there is no reason to assume that humans would be more or less susceptible than the rat. As with many other carcinogens, there are no interspecies differences in metabolism that would provide information on possible differences in the direction or magnitude of carcinogenic responses.

Topic 2. Future Studies

Information is needed on relationships between ambient formaldehyde levels in air and its concentration at target cells.

Effects of airborne formic acid should be studied to see whether it may be responsible for formaldehyde effects.

Information is required on penetration, transport and tissue distribution of inhaled gaseous formaldehyde and the time course of formaldehyde concentration in blood and tissues after administration by various routes.

Comparative studies on related aldehydes would be desirable to reveal their toxic effects, metabolism and reactions with macromolecules.

There is a need for human studies and for a model of the human upper respiratory airway system to determine rate constants for absorption, transport, and metabolism. This should include studies of formaldehyde bound to airborne particulates.

Information is needed on degranulation of rough endoplasmic reticulum caused by formaldehyde and its effect on the membrane thiol–disulfide exchange enzymes.

Other questions concern whether chromosome breaks are related to formaldehyde dose; whether formaldehyde induces DNA repair enzymes and mixed function oxidases in nasal epithelium; whether the nasal carcinogen, hexamethylphosphoramide is carcinogenic systemically and whether abnormal dietary fatty acids can so alter membrane structure as to affect cross-linking in glutathione-depleted animals.

It would be desirable to learn whether modification of glutathione concentration affects toxicity of formaldehyde *in vivo* and *in vitro*.

The following questions emerge: Does exposure to airborne formaldehyde lead to excretion of mutagens in the urine? What are the structures of the modified bases in DNA–formaldehyde adducts? What are the nature and degree of inhibition of DNA repair after modification by formaldehyde?

Reproduction/Teratology Panel Report*

Topic 1. Is there evidence that formaldehyde produces reproductive toxicity or is teratogenic in experimental animals or man?

a. Is there evidence that formaldehyde causes germ cell mutations in experimental animals which are clinically significant?
b. If there is evidence for reproductive or teratogenic effects, are there biological models to explain the activity?
c. Is there evidence for reproductive or teratogenic effects from substances related to formaldehyde or known to be metabolized to formaldehyde?

Topic 2. What experimental or epidemiologic studies would be important to resolve any controversies in this area?

Topic 1. Reproductive Toxicity

There is a paucity of data addressing possible reproductive and developmental hazards of formaldehyde in experimental animals or man. Our answers to the questions posed about adverse reproductive effects should be viewed as far from conclusive regarding either the safety or lack thereof due to exposure to formaldehyde.

There has been one adequate study of possible teratogenic effects in mammals. Marks and colleagues (*212*) intubated pregnant mice on days 6 through 15 of gestation with 0, 74, 148 or 185 mg/kg/day. At the highest dose, 22 of 34 pregnant mice died. At that dose, there was an increased incidence of resorptions, but that increase was not statistically significant. At no dose did the incidence of malformations differ between the treated and control groups. There were also no treatment-related differences in the mean number of implantations, stunted fetuses, live fetuses per litter, or average fetal body weight per litter. At a dose which killed more than 50% of the dams, no adverse reproductive outcomes were observed except for the increase in the incidence of resorptions that was not statistically significant.

1c. Although the Marks study (*212*) exposed animals to high enough doses to kill the dams, it is not likely that embryos were exposed to formaldehyde itself due to the very short biological half-life (*142*). Another approach used to investigate whether formaldehyde is teratogenic has been to give hexamethylenetetramine (HMT), which is metabolized to formaldehyde *in vivo*. Hurni and Ohder (*213*) exposed pregnant beagle dogs to 1250, 600 or 0 ppm HMT in the feed during days 4 through 56 of gestation. At 1250 ppm, 10 of 56 pups were stillborn, the growth rate between birth and weaning was decreased, and there was an increase in early postnatal mortality. There were no malformed pups. In a study in rats by Della Porta et al. (*214*), exposure to HMT at 1% in drinking water from 2 weeks before pregnancy through weaning produced no malformed animals. Pups drinking the same solution after weaning had a temporary decrease in weight gain. In a two-generation study by Natvig et al. (*215*), rats fed a diet of 1600 ppm HMT (100 mg/kg/day) showed no difference in weight gain or fertility in the first or second generation. Staples (*216*) reviewed studies involving hexamethylphosphoramide. This compound did not cause reproductive problems in rats gavaged with up to 200 mg/kg/day or by inhalation of 0.334 ppm. Staples (*216*) also indicated that glycerol formal (a condensation product of glycerin and formaldehyde) has been reported to be teratogenic in rats after administration subcutaneously or intramuscularly at all dose levels tested from days 6 through 15 of gestation. The panel is not aware of any human exposure or if this compound is metabolized to formaldehyde *in vivo*.

1. Other adverse reproductive effects were reported by Hagino (*217*), who found prolonged diestrus, but no impairment of reproductive function in female rats stressed with strong formalin vapor (concentration not specified). Ovarian involution and endometrial atrophy were found in female mice exposed to 40 ppm formaldehyde by inhalation—an exposure level that killed 80% of the animals (*211,218*). The panel members reviewed several other studies in experimental animals (*216,219*) and agreed that there were sufficient methodologic problems to render them of little value.

The human data are extremely meager. Shumilina (*220*) studied workers exposed and not exposed to

* Reproduction/Teratology Panel: Godfrey P. Oakley, Jr. (Chairman); Rochelle Wolkowski-Tyl (Alternate Chairman/Secretary); Sarah H. Broman; Thomas F. Collins; Carole A. Kimmel; Thomas A. Marks.

urea–formaldehyde resins. Concentrations of 1.2 to 3.6 ppm formaldehyde were observed in the exposed groups. The methods of data collection were not very well explained in the translated article, so that the panel had many questions about methodology and the interpretation of these data. The author concluded that exposed women had a three-fold increase in menstrual disorders and produced more babies with birth weights between 2500 and 3000 g than did controls. However, the panel noted that only a few neonates weighed less than 2500 g and the rates did not differ for exposed and nonexposed women. The panel members did not view this evidence as very strong since many factors that could not be evaluated from the report could have explained the finding. In a better designed survey, Olsøn and Døssing (*77*) found that 30% of women working in an environment of 0.43 mg/m^3 formaldehyde had a history of menstrual irregularities, whereas a reasonably matched control group had no history of menstrual irregularity. The exposed women reported eye irritation, headache and use of analgesics more frequently than did controls. The panel felt that these two papers, rather than showing a cause-and-effect relationship between formaldehyde exposure and menstrual disorders, point to a reproductive effect that needs further evaluation.

Hemminki et al. (*221,222*) studied spontaneous abortions among hospital staff engaged in sterilizing instruments with chemical agents. They reported no increase in spontaneous abortions associated with use of formaldehyde.

There is indirect evidence that would argue against formaldehyde being a major human teratogen. Over the last 30 years, the annual production and domestic use of formaldehyde in the United States has gone up fivefold from one billion pounds to about five billion pounds. Birth defects have been reasonably stable over the last 30 years, although in the last decade, there have been some exceptions to this rule. The reported incidence of ventricular septal defects and patent ductus arteriosus has increased and that of anencephaly and spina bifida has declined (*223*).

1a. Panel members did not find evidence of germ-cell mutations of clinical significance in mammals. One study by Fontignie-Houbrechts (*113*) indicated an increased pre- and post-implantation loss in the first week of mating, following exposure of males to 50 mg/kg by injection, and increased preimplantation loss in the third week. However, Epstein et al. (*112*) found no evidence of increased dominant lethal effects in mice exposed at doses up to 40 mg/kg, IP. Cassidy (*224*) reported increased sperm abnormalities in rats following exposure to 200 mg/kg, but not to 100 mg/kg, given orally. Thus, the data are not consistent and do not adequately test the possibility that formaldehyde causes germ-cell mutations.

Human germ-cell mutations causing nondisjunction could result in an increase in Down's syndrome. The constancy of maternal age-specific rates of Down's syndrome over the last 30 years, in face of increased exposure, suggests that exposure to formaldehyde is not causing nondisjunction in humans (*225*).

In summary, the panel could find no evidence clearly demonstrating that formaldehyde caused adverse reproductive outcomes. What it found was a paucity of information from which to make inferences and data that suggested hypotheses to be tested in future studies. This panel feels that formaldehyde poses little, if any, risk as a potential human teratogen. This judgment is based on the irritation potential of formaldehyde at extremely low ambient concentrations (0.05 ppm), existing data from *in vivo* mammalian studies, and toxicokinetic and metabolism data indicating an extremely short half-life (not detected to 1.5 min) of the parent compound, and relatively short half-life (80 to 90 min) of the only known metabolite (formate) in the blood, regardless of the route of exposure (*142*).

Topic 2. Future Studies

Animal Studies. There was consensus that no adequate reproductive studies exist using inhalation exposure which is the primary route of human exposure. The panel has no toxicokinetic information to suggest that inhalation studies would actually result in exposures as high as in the intubation study which was negative (*212*). However, classic teratology studies using inhalation exposure would resolve the question of teratogenicity with such exposure. We understand that such a teratology study is being initiated soon in Canada (Dr. W. J. Martin, Chairman, Formaldehyde Council of Canada, communication to the panel). In addition, the panel believes it would be reasonable to do the following studies: combine or modify several existing protocols to evaluate reproductive effects; sperm morphology and vaginal cytology (*226*); fertility assessment by continuous breeding (*226*); evaluate animals at the end of the continuous breeding experiment to seek signs of functional impairment in offspring.

If data from the above experiments indicate reproductive and/or developmental risk, further studies should be performed. Studies should be done to investigate possible differences in the kinetics and metabolism of formaldehyde with differing routes of exposure in experimental animals. These studies should provide data for comparison between animal studies and human exposure data for risk assessment.

Epidemiology Studies. There are several possible epidemiologic approaches to studying the relationship between formaldehyde and adverse reproductive outcomes. In one approach, a group of exposed women and a group of unexposed women would be located and adverse reproductive effects sought. Women who might have or had industrial exposures and women who live in house trailers would be reasonable subjects for such a study. If such a study were to be done, every effort should be made to determine whether menstrual irregularity resulted from exposures. The panel realizes that a great deal of care will be needed in the design and

execution of this study if a valid answer is to be found. Other reproductive outcomes should be studied. The panel realizes that a very large number of subjects will be needed to get a reasonable evaluation on whether exposure causes birth defects or developmental delays. Evaluation of the rate of low birth weights should be feasible.

Paternal exposure could be causing adverse reproductive outcomes. Studies of male workers and controls would evaluate this possibility.

A more practical and cheaper way to seek to identify human reproductive outcomes associated with exposure is to seek histories of exposures where there have been adverse reproductive outcomes. The panel suggests that existing case-control studies of birth defects be reviewed for evidence of exposure. The panel believes it would be reasonable to do a case-control study of birth defects specifically seeking relationships with exposure.

Behavioral/Neurotoxicity/ Psychological Effects Panel Report*

Topic 1. What is known about the effects of formaldehyde on the biochemistry and/or morphology of the nervous system?

Topic 2. Does formaldehyde induce behavioral or psychological changes? If so, what is the evidence and what methods can be used to measure the changes?

Topic 3. What critical experimental questions remain? What epidemiological studies might be important in this area?

1. Effects of Formaldehyde on the Biochemistry of the Nervous System. Not much work has been done on the effects of formaldehyde on the biochemistry of the nervous system. Heck et al. (*227*) have shown that there was radioactivity in the brain after the animals were exposed to ^{14}C-formaldehyde for 6 hr. The concentration of radioactivity in brain after exposure of F-344 rats to airborne ^{14}C-formaldehyde for 6 hr (formaldehyde concentration range 5–24 ppm) was 0.37 (dpm/g tissue/dpm/g plasma), compared to 4.95 in the esophagus and 2.05 in lung. The chemical nature of the radioactive labeled compound remained to be studied. It is unlikely to be formaldehyde itself because it is a very reactive compound. Since formaldehyde readily forms condensation products with a number of biogenic amines, it is possible that these condensation products may be found in the brain. This aspect has been reviewed by Golberg (*228*). Another possibility is that formaldehyde may be converted rapidly to formic acid. The latter may join one-carbon metabolism by the tetrahydrofolate pathway, and in turn be incorporated into amino acids such as methionine and serine (*229*). Formation of methionine could account for the labeled choline observed by DuVigne et al. (*230*).

1. Neurochemical Studies. Formaldehyde is mainly metabolized to formate. Formate anion is an inhibitor of cytochrome oxidase (*231–233*) and the inhibition of cytochrome c oxidase by formate increases with decreasing pH. Because of man's evolutionary loss of the enzymes uricase and formyltetrahydrofolate reductase, man cannot utilize formate in many syntheses via the folate pathway (*234*). This enhances the human toxicity of chemicals that are metabolized to formate. The central nervous system is especially vulnerable to hypoxia which may be a relevant feature quite apart from acidosis in possible nervous system toxicity of formaldehyde (*235*).

Exposure to formic acid vapor (20 ppm for 3 and 8 days, 6 hr daily) caused increased cerebral acid proteinase activity in rats (*235*). Cerebral glutathione increased initially, probably as a reactive phenomenon, but decreased at 8 days with increased acid proteinase activity, both reflecting increased lipid peroxidation (in cerebral hypoxia). Acid proteinase activity in cell fractions increased above the control range during the third week of exposure to rats to 20 ppm of formic acid vapor 5 days/week, 6 hr daily (*236*). Hypoxic labilization of the lysosomal complex was suggested as an explanation for the finding.

Dimethylformamide, a general solvent in industry, is demethylated *in vivo* to produce monomethylformamide and formaldehyde (*237*). When rats were exposed through drinking water to 13.7 mM dimethylformamide, acid proteinase activity increased in the glial cell fraction after 2 and 7 weeks while under the same conditions cerebral glutathione concentration was below the control range (*238*).

High concentrations of formaldehyde (196 ± 32 ppm), moderate levels of formic acid (11 ± 3 ppm) and low concentrations of acrolein (0.07 ± 0.03 pm) were detected in the air containing oxidative thermodegradation products of polyacetal plastic (Deldrin, DuPont) (*239*). Rats were exposed to this mixture for 6 hr, once or three times. They gasped for air for hours after the exposure. The fumes decreased the cerebral RNA concentration, together with decreases in the succinate dehydrogenase and acid proteinase activities.

Irritant Action of Formaldehyde on Sensory Nerves. 1. The effect of exposure to formaldehyde was studied in anesthetized rats by Kulle and Cooper (*239*), who judged the response by an increase in action potential firing rate of nasopalatine and ethmoidal nerves of the trigeminal nasal sensory system. Brief (2 min) exposure over a range of 0.5–2.5 ppm formaldehyde delivered through a nose cone yielded responses like those elicited by ozone and amyl alcohol. Exposure to 0.5, 1.0, 1.5 or 2.0 ppm formaldehyde for 1 hr, repeated up to four times, revealed a progressive depression in the response to amyl alcohol with increasing formaldehyde concentration. The effects of a 2.0 ppm exposure were similar whether presented separately or as the final exposure of a series. Return to air inhalation for 1 hr brought about a partial recovery of the neural response to amyl alcohol.

* Behavior/Neurotoxicity/Psychological Effects Panel: Leon Golberg (Chairman); Marc Schenker (Alternate Chairman/Secretary); Jean Chen Shih; Michael J. Colligan; Anna Seppalainen.

The authors assert that even 1.0 ppm formaldehyde elicits "a significant depression in the rat trigeminal nerve response to a standard odorant." However, it is important to realize that the rats were under urethane anesthesia and had been treated with atropine before surgery, with further supplements as required to limit the production of mucus. Similar exposure to 5 ppm ozone for 1 hr actually increased neural responsiveness to amyl alcohol.

There is a considerable body of information on the acute irritant effects of formaldehyde on healthy human subjects. In one such study, Weber-Tschopp et al. (*202*) reported that irritant effects such as eye blinking rate as well as subjective irritation and annoyance increased as a function of formaldehyde concentration. The threshold for such effects was judged to lie between 1 and 2 ppm.

1c. MORPHOLOGICAL CHANGES IN RESPONSE TO FORMALDEHYDE EXPOSURE. Potts et al. (*240*) injected formaldehyde intravenously over several hours to achieve a total dose of 0.9 g/kg in monkeys. No histologically detectable effect was observed in the central nervous system. On the other hand, Bonashevskaya (*241*) reported lesions in the cerebral amygdaloid complex after exposure to formaldehyde. Structural and cytochemical shifts occurred in the amygdaloid complex of rats after 3 months at 1 to 3 mg/m^3 formaldehyde in hermetically sealed chambers. The shifts were described as "disturbed uniformity" in the content of Nissl bodies and RNA in the limits of the same amygdaloid nucleus. Some neurons showed extensive accumulation, and others reduction of these constituents. Measures taken to monitor the concentrations of formaldehyde in the exposure chambers were not reported.

2. A number of reports exist which link chronic formaldehyde exposure to a range of psychological/behavioral problems including depression, irritability, memory loss and decreased attentional capacity, and sleep disturbances. Unfortunately, these studies, reviewed by Sauer (*242*), for the most part have involved field surveys using subjective self-report symptom inventories. Control data, describing the incidence of such symptoms from unexposed cohort samples, are often inadequate or completely absent. This is an extremely thorny problem when dealing with formaldehyde, which in addition to any direct toxic effects possibly associated with it, produces distinct olfactory cues which when detected by the individual may stimulate a spectrum of secondary psychological reactions (e.g., expectancies, irritations, anxieties, fears, etc.). These reactions may in turn exacerbate, mask, or interfere with the more direct neurologic, biochemical, and physiological responses to the substance.

For purposes of exposition, this suggests that formaldehyde may affect the psychological functioning of the individual in three ways: (1) directly, as a result of the immediate toxic properties of the substance on the peripheral and central nervous systems; (2) indirectly, as a result of the individual's monitoring and awareness of the aforementioned changes and his/her interpretation and reaction to such changes, which, in turn, feeds back into the central nervous system; and (3) as a result of the individual's psychological reaction and concomitant CNS response to the olfactory properties of the substance. In practice, these processes are interdependent, yet this simple analysis of a complex series of responses underlines the need to control for "expectancy" effects in formaldehyde research to permit a differentiation of the direct effects of formaldehyde on psychological functions from its secondary effects.

EPIDEMIOLOGIC CONSIDERATIONS. Several epidemiologic studies have evaluated neuropsychological symptoms potentially due to occupational or environmental exposure to formaldehyde (*243–245*). While a high prevalence of symptoms has frequently been observed and ascribed to formaldehyde, serious deficiencies in study design, assessment of exposure and outcome measurement limit the interpretation of these studies.

Dally and co-workers reported symptoms prevalences among residents of homes in Wisconsin that had health-related complaints, possibly due to formaldehyde exposure (*243*). The median formaldehyde concentration was 0.47 ppm (range $<$ 0.1–3.68 ppm) and a positive (inverse) association was present between age of the structure and formaldehyde concentration. The greatest prevalence of symptoms was for irritation of mucous membranes, but of the 256 subjects, 53% reported headaches and 38% reported difficulty in sleeping.

The major weakness in this study is selection bias of the population, i.e., only subjects from homes where complaints were registered were studied. An appropriate control population was not included. Responses may also have been biased by other considerations such as reports in the press and ongoing litigation. No attempt was made to evaluate respondent bias nor were responses related to measured levels of formaldehyde or other potential covariates collected during the investigation.

Similar criticisms exist for the studies of Sardinas et al. (*244*) and Garry and co-workers (*245*). Both of these investigations, in Connecticut and Minnesota, respectively, found a high prevalence of headache but failed to include control populations or account for selection bias. A report of symptoms in 20 infants under 12 months of age by Woodbury and Zenz (*246*) also found frequently reported problems with sleeping (14/20), but no association was present with measured concentrations of formaldehyde and this study suffers from the same biases as the adult studies.

Thun and Altman (*78*) have pointed out some of the difficulties in prevalence surveys of symptoms in residents from homes with urea–formaldehyde insulation (UFFI) foam, including the presence of odor affecting response, respondent and recall biases, and the objective outcomes measured. In this case-control study, no significant difference was found in the occurrence of headaches or insomnia in residents of homes with UFFI, compared to neighborhood controls (*247*).

A controlled evaluation of symptom prevalence was undertaken by Olsøn and Døssing (*79*). They administered a questionnaire based on the linear analogue

self-assessment method to 66 subjects who worked in a mobile day care center and 26 controls working in permanent centers. Mean concentrations of formaldehyde were 0.43 and 0.008 mg/m^3, respectively, with no difference in temperature, humidity or ventilation rates. A significantly greater prevalence and greater symptom intensity of nose and throat irritation, unnatural tiredness, and headaches was present in the exposed subjects. No difference was noted in disturbed memory or concentration or in the control questions on the questionnaire. This study overcomes some of the previously mentioned problems, but responses still may have been influenced by awareness of the subjects of the study goals and hypotheses. Nevertheless, this is a controlled study using a standardized questionnaire and the findings need further investigation.

Reported symptoms need to be evaluated by formal tests of neuropsychologic function. Schenker and co-workers (*248*) found in a pilot study that residents of homes with UFFI who complained of memory impairment did not have abnormalities on formal tests of memory function, although many showed deficits in tests of attention span or the ability to sustain attention. This result needs to be evaluated in a controlled, population-based study.

One study has briefly considered neurologic functioning in a controlled laboratory exposure. Anderson (*124*) reported on 16 healthy young subjects to 0.3, 0.5, 1.0 and 2.0 mg/m^3 formaldehyde for 5 hr. He found subjective and physiologic responses with exposure, but no effect on performance tests (speed and accuracy of multiplication and addition, and of card punching) at any of the exposure concentrations. Details of the performance tests were not presented, and the power of the study was not reported.

A preliminary report by Kilburn and co-workers (*249*) described a study using a standardized battery of neuropsychological tests on histology technicians. Subjects were also exposed to xylene and toluene at work, and there was no measurement of individual exposures. Response rates and characteristics of the exposed and control populations are not reported, and no consideration was given to potential respondent bias in symptoms or exposures. No data are presented on the tests of neuropsychologic function. This study utilizes standardized tests of neuropsychologic function, but the results cannot be considered indicative of effects due to formaldehyde exposure.

Conclusions. The effects of formaldehyde and/or its metabolites on the biochemistry of the nervous system have not been clearly defined. Various possibilities exist whereby such effects might be mediated.

Some evidence exists that exposure to formic acid (the principal metabolite of formaldehyde) in vapor form at high concentrations exercises nervous system toxicity in intact rats.

The irritant effects of formaldehyde may be reflected in altered function of sensory nerves such as the trigeminal nasal sensory system. The presence of morphological changes in the CNS has been observed in one study and not in another.

The difficulties inherent in any study of psychological/behavioral effects of formaldehyde have not yet been overcome in the course of conducting field surveys.

Epidemiologic studies evaluating neuropsychological symptoms potentially due to occupational or environmental exposure to formaldehyde have failed to overcome the problems commonly associated with such studies. However, some studies merit further investigation.

Topic 3. Future Studies

Biochemical. While the neurotoxicity of formaldehyde is still a controversial issue, the study on the biochemical effect of formaldehyde on the central nervous system will provide fundamental knowledge for understanding its possible neurotoxicity.

Effort should be made to identify and to characterize the structure of the radioactive compound found in rat brain after the animals were exposed to ^{14}C-formaldehyde. Radioactive formate, radioactive choline and radioactive condensation products between biogenic amines and formaldehyde are the possible compounds. Among these compounds the condensation products are of particular interest. Tetrahydrobetacarboline should be found if indoleamines and formaldehyde formed a condensation product. Tetrahydroisoquinolines should be found if catecholamines and formaldehyde form condensation products.

Once the structures of the radioactive compounds have been determined, the distribution of these compounds in brain, the effects of these compounds on neurotransmitter receptors, uptake, biosynthetic and degradative enzymes could be systematically studied. Furthermore, the effects of those compounds on animal behavior could be examined.

Electrophysiological. Acute effects of formaldehyde have been studied on the trigeminal nasal sensory system (*239*). Several authors (*250,251*) have suggested that electrophysiological methods of studying the central nervous system are helpful in evaluating toxic effects of, for example, formaldehyde. Long-term experimental exposure to various concentrations of formaldehyde could be carried out on rats and/or rabbits and electroencephalography (EEG) with indwelling electrodes in hippocampal and cortical (occipital) areas could be performed. Spontaneous EEG activity could be analyzed at various time intervals during the exposure and evoked potential studies using flash light stimulus (visual evoked potentials) as well as sound stimulus (brainstem auditory evoked potentials) could and should be applied at various intervals of continous exposure.

No studies have demonstrated peripheral nervous system effects of formaldehyde. Possible PNS effects could be checked by applying nerve conduction measurements in chronically exposed rats.

Given the fact that a sound, systematic data base

describing the impact of formaldehyde on psychological/behavioral functioning is currently nonexistent, it was agreed that considerable research is needed along these lines. Furthermore, it was felt that the primary emphasis should be placed on long-term, or prolonged exposures to disentangle the potential toxic effects of formaldehyde from the transient, irritative ones, and to simulate the exposure conditions of relevant populations at risk in the environment, such as inhabitants of mobile homes having urea–formaldehyde insulation and individuals experiencing working-life occupational exposures. The emphasis on chronic exposure studies suggests two particular research paradigms: (1) animal studies in which controlled, measured doses of formaldehyde are administered over variable periods of time to assess the effects on select, well-defined behavioral and performance parameters; and (2) field/epidemiological studies in which groups of people undergoing long-range, measurable formaldehyde exposures as part of their daily routine (e.g., medical students, anatomists, plywood/fiberboard workers, mobile home dwellers) are assessed in terms of relevant psychological/behavioral parameters relative to appropriate baseline-exposed cohort samples.

With respect to the animal studies, it was felt that the test battery should encompass a range of measures involving relatively simple and direct sensory responses (e.g., absolute and difference sensory thresholds), motor behaviors (e.g., balance and tremor assessments), sensory-motor activities (reaction times, avoidance learning, etc.) and cognitive processes (short- and long-term memory, discrimination learning, etc.). Information stemming from this research will identify system-specific as well as general responses to formaldehyde, and help to identify parameters for follow-up research in the human field studies. With respect to the latter, given the limited knowledge regarding the impact of formaldehyde on human psychological/behavioral functioning, it was felt that a broadbrush approach was most appropriate. The human performance test battery should assess an array of psychological functions ranging from relatively simple sensory responses (e.g., threshold determination, attention, vigilance) through perceptual motor operations (e.g., simple and choice reaction times, tracking, short-term memory) to complex cognitive operations (e.g., concept formation, dual-task strategies, logical reasoning). Visual evoked potential (VEP) recordings could be accommodated to study acute effects in the visual sensory system.

Workers handling formaldehyde containing material might be locally exposed through the skin. This could induce local neurotoxic effects in peripheral nerves. Inhalation exposure could in the long-term also affect the peripheral nervous system (PNS). As the distal ends of long nerves are usually the first portions to suffer in chemical neurotoxicity the PNS should be checked upon. A feasible approach could be to measure the distal sensory conduction velocity from fingers to wrist in the arm nerves. Measurements of the amplitude of the elicited sensory action potential might increase the sensitivity of the method. Such a battery of tests could be coupled with traditional paper and pencil tests (e.g., Wechsler Intelligence Scales) for which there are standardized population norms, but it is felt that the critical comparison is against a cohort of base-line exposed controls comparable to the target group along relevant socioeconomic, educational, and occupational dimensions.

Traditional psychodiagnostic inventories of psychopathology (e.g., MMPI, Beck Depression Scale) or mood state (e.g., Profile of Mood States) would also be appropriate. Cross-sectional designs should attempt to identify not only "exposed" and background or baseline-exposed cohorts, but should attempt to quantify the level and duration of exposure for all groups to permit maximum statistical analysis. Prospective studies, if feasible, should involve repeated testing of both the target and control cohorts to control for aging and historical effects.

Finally, attempts should be made to gather "real-life data" (e.g., academic performance, sleep diaries, behavioral sampling) to complement the psychological testing. Occupationally and environmentally exposed populations should be studied because they provide a unique opportunity to investigate the potential neurotoxicity of formaldehyde. Such studies allow investigation of sensitive populations (e.g., children), long-term exposures, and acute exposures at formaldehyde concentrations that cannot be used in a controlled laboratory setting. It is important that appropriate control populations be included in these studies and adjustment be made for potential confounders such as socioeconomic status. The studies should include a spectrum of neuropyschological tests, including standardized and validated tests when possible. Attempts are currently underway to develop such a test battery, and similar studies have been done on working populations with exposure to solvents or heavy metals. A difficult and expensive component of such studies is the measurement of formaldehyde exposure, but such measurements are an important component of epidemiologic investigations. Several occupational populations exist that represent possible study groups. Medical students or other users of anatomy and pathology laboratories could be studied to evaluate effects of short term exposures (3–6 hr) on neuropsychologic test performance. The fabric industry uses formaldehyde in coating certain products and appropriate unexposed comparison groups may exist within the industry to allow controlled evaluation of workplace exposure. Numerous other industries have workplace exposure to formaldehyde and should be evaluated for the nature of the formaldehyde exposure and the feasibility of epidemiologic investigation. Home exposures to formaldehyde may occur from insulation products or from building materials themselves. Some schools may have elevated formaldehyde exposures because of new construction or from the use of trailers

for classrooms. These situations allow the design of controlled epidemiologic studies to evaluate behavioral/neurotoxicologic/developmental effects among large populations including young children. Similar studies have been performed to evaluate neuropsychologic effects, in children, of lead toxicity or dietary alterations.

Risk Estimation Panel Report*

Topic 1. How can all the available data be integrated to make reasonable risk estimates (neoplastic and nonneoplastic) for humans exposed to formaldehyde at various levels and through different routes?

a. In making estimates, what data and assumptions lead the Panel to choose one method over another?
b. In making risk estimates, how can data be used from:
   1. metabolism studies
   2. biological endpoints (importance of benign tumors)
   3. individual variabilities
   4. epidemiology
   5. high or low dose extrapolation models
   6. interspecies variation

Topic 2. Are any practically achievable data likely to resolve any of the uncertainties?

Risk assessment is generally regarded to consist of three main functions: hazard identification, exposure assessment, and risk estimation. Hazard identification is the qualitative determination of an actual or potential toxic effect in humans or in animals that is also presumed to pose a threat to humans. This includes identifying toxic biological endpoints, investigating mechanisms that may alter the response in humans, and identifying data sources that may be useful in performing quantitative risk assessments. Hazard identification also involves the determination of the degree of the hazard, i.e., is it life threatening or not; reversible or not. These topics were addressed by the other panels at the workshop. Exposure assessment is the activity of identifying the routes and extent of exposure of the human population to toxic substances. This function involves identifying sources of toxic substances, exposure levels, and length of exposure, which may be occupational, environmental, or from consumer products, which may be intermittent or continuous. These levels of exposure may be used in time-dose-response functions to estimate risks (the animal or human probability of a toxic health effect by a specific age or the average time without a toxic response). The expected number of individuals with a disease in a population requires estimates of the numbers of individuals in various exposure groups multiplied by the probability of disease for those groups.

Risk estimation is the quantitative aspect of risk assessment which attempts to mathematically relate risk to exposure. In some instances, this can be done with human data. Generally, only animal data are available. Since it is necessary to determine if there are toxic effects using relatively small numbers of animals, doses well above human exposure levels are generally employed in animal bioassays. The process of quantitative risk estimation usually involves two main functions: (1) extrapolation of risks from high to low doses and (2) extrapolation of risks from animal exposures (e.g., laboratory animals exposed to a constant level continuously for life) to human populations that are genetically and environmentally heterogeneous and exposed to varying levels at various times during their life.

1. The first task of the Risk Estimation Panel was to review the reports from the other panels to establish what potential risks to human health exist due to exposure to formaldehyde. The second task was to identify time-dose-response data sets that could be used for quantitative risk estimation of formaldehyde. The third task of the panel was an attempt to utilize whatever biological and mechanistic actions of formaldehyde were identified by the other panels to assist in the choice of time-dose-response models for low dose risk estimates.

1b.2. Immunology/Sensitization/Irritation. Formaldehyde produces irritation of the nose, eyes and throat when inhaled, and of the skin when applied topically in solution. In most individuals, this is simple irritation and not due to an allergic reaction. However, the Immunology/Sensitization/Irritation Panel found that allergic contact dermatitis and other forms of skin sensitization did occur in some individuals. There was not sufficient evidence to confirm that respiratory tract allergy occurred, although there were some suggestive findings.

There were difficulties in assessing the proportion of individuals who were unduly sensitive to skin contact. Data were also inadequate to establish clear threshold doses for the various effects. For normal individuals, it was possible to give a range of doses over which various harmful effects were seen, but there generally were not adequate dose-response data.

In view of the frequent lack of data on dose-response and on the proportion of individuals who are unduly sensitive, the Risk Estimation Panel did not attempt at present to perform a quantitative risk estimation for the irritant or sensitization effects of formaldehyde, although some risks clearly exist at some current levels of exposure.

1b.2. Behavior/Neurotoxicity/Psychological Effects. The Behavior/Neurotoxicity/Psychological Panel reported that exposure to formaldehyde produced neurochemical changes in the brain of rats, and also possible effects in peripheral nerves but further studies of these phenomena were needed.

In humans, there have been reports of various symptoms in subjects exposed to formaldehyde either in

* Risk Estimation Panel: David Gaylor (Chairman); Mary F. Lyon (Alternate Chairman/Secretary); Roy Albert; Charles C. Brown; Murray S. Cohn; Robert Sielken, Jr.; Mike Wright.

the home or at work. However, there was great difficulty in interpretating these data. In some cases, there were no adequate controls. In other cases, the possibility of subjective effects due to the smell of formaldehyde could not be excluded. Commonly, the exposure level was not known.

In view of the difficulties and uncertainties in these studies, the Risk Estimation Panel feels that there are no adequate data for attempting to assess quantitative risks of behavioral or psychological effects resulting from formaldehyde exposure in man at the present time.

1b.2. Reproduction and Teratology. The data concerning adverse effects of formaldehyde on reproduction and on fetal development were reviewed by the Reproduction/Teratology Panel. Data on possible induction of germ cell mutations were considered by both the Reproduction/Teratology Panel and the Carcinogenicity/Histopathology Genotoxicity Panel.

The Reproduction/Teratology Panel found no clear evidence of any adverse effects of formaldehyde on either reproduction or development of the fetus. However, there were grounds for suggesting that further work was needed to elucidate certain points.

Concerning mutation in mammalian germ cells, both the Reproduction/Teratology Panel and the Carcinogenicity/Histopathology/Genotoxicity Panel found no good evidence of positive effects. The Carcinogenicity/Histopathology/Genotoxicity Panel recognized formaldehyde as a weak mutagen, and both panels noted one study in which marginally positive results were obtained in a dominant lethal test. However, the mouse spot test was negative. This led the Carcinogenicity/Histopathology/Genotoxicity Panel to conclude that more extensive tests of mutation in mammalian germ cells were not at present warranted.

On the basis of these findings, there are no grounds at present for attempting any quantitative estimates of risk to humans for adverse effects on reproduction, fetal development, or hereditary defects resulting from exposure to formaldehyde.

1b.2, 1b.3, 1b.4. Epidemiology. In comparing the results of experimental animal studies to human epidemiological observations, there is evidence that the affected site in animals is not necessarily predictive of the affected site in humans.

The Epidemiology Panel stated that there is some evidence of a dose-response relationship between formaldehyde exposure and lung cancer based upon the one of six British factories where the largest number of cohort workers experienced the highest formaldehyde exposure levels. The Risk Estimation Panel noted that sufficient epidemiological data are not now available for a quantitative risk estimate which relates the level and duration of formaldehyde exposure to the risk of either lung or nasal cancer.

Studies of three professional groups who preserve human tissues with solutions containing formaldehyde and other chemicals have shown an excess of brain cancer and leukemia. The Epidemiology Panel suggested further investigation of the questions raised. No dose-response information is currently available for quantitative risk estimation.

The Risk Estimation Panel recommends that no quantitative risk estimate be based on the current epidemiological information. However, we also recommend that future estimates might be based on additional data provided by further analyses of these human populations.

In addition, we recommend that the results of risk assessments based on animal studies should be compared to the information from each of these human observational studies in order to evaluate the extent to which there is any statistical consistency or inconsistency of this extrapolation to human data.

1a, 1b.2. Endpoints for Risk Estimation. The Risk Estimation Panel found that data from the CIIT rat inhalation chronic bioassay are suitable for modeling the dose-response relationship. The data from the formaldehyde studies in Syrian hamsters and the CIIT mouse inhalation study provide information on risk, but do not provide sufficient dose-response information for quantitative model fitting. The panel agrees with the conclusion of the Carcinogenicity/Histopathology/Genotoxicity Panel that the malignant tumors represent an endpoint which should be used in any quantitative risk assessment based on the CIIT rat inhalation data. The Risk Estimation Panel follows the Carcinogenicity/Histopathology/Genotoxicity Panel recommendation that, because of different cell types of origin, any evaluation of polypoid adenoma be done separately from squamous cell carcinomas. The Risk Estimation Panel also agrees with the Carcinogenicity/Histopathology/Genotoxicity Panel that nonneoplastic polyps and hyperplasias do not at present represent endpoints suitable for the assessment of tumor risk. The Carcinogenicity/Histopathology/Genotoxicity Panel noted the difficulty of differentiating between polypoid adenomas, nonneoplastic polyps, and hyperplasia, in the CIIT rat inhalation study. A recently completed re-examination by a Pathology Work Group resulted in diagnoses that were in close agreement with the original diagnoses of polypoid adenomas. Papillomas, which are generally considered to be the benign counterpart of the squamous cell carcinoma, were not seen in the CIIT rat inhalation study. Nasal adenocarcinomas were seen in the NYU formaldehyde study. The data now available lead the Risk Estimation Panel to believe that the target sites of formaldehyde are not primarily distant from the site of exposure.

1a, 1b.1, 1b.6, 1c. Species-to-Species Extrapolation. Risk estimation, when based on animal data, must consider the relationship between risk observed in the test species and risk projected in the species of concern (*252,253*). In the case of formaldehyde, humans are the species of concern and the test species used in the quantitative modeling techniques are the rats in the CIIT chronic inhalation study. Species differences have been observed with respect to factors which may influ-

ence carcinogenic risk. An example comes from the CIIT study itself, where at high concentrations of formaldehyde, mice modify their respiration more than rats.

There are, however, no indications that the response by humans would be different than that exhibited by rats, mainly due to the lack of experimental data pertaining to this issue. Qualitatively, the metabolic pathways of formaldehyde in rats and humans are similar. The sites of greatest exposure may differ, since rats are obliged to breathe solely through the nose and humans may also breathe orally. Again, no information exists demonstrating that the response would be quantitatively different as a result of differences in distribution of the inhaled dose.

The panel recommends that the suggestion of the Structure Activity/Biochemistry/Metabolism Panel be utilized in risk estimation: "Although there are differences in formaldehyde carcinogenicity among different species, at present there is no reason to assume that humans would be more or less susceptible than the rat." The panel can only assume that rats and humans exposed to the same concentration of formaldehyde for the same proportion of lifetime will exhibit a similar carcinogenic response, all other influences being equal. The panel recognizes that this assumption is based on the lack of information and may change as further data become available.

The Structure Activity/Biochemistry/Metabolism Panel noted that the nonlinear carcinogenic response to dose observed in the CIIT Study was in contrast to the linear response of DNA–protein crosslinks at 6 ppm and above. The Carcinogenicity/Histopathology/Genotoxicity Panel considered impairment of mucociliary clearance, detoxification, and DNA repair as leading to relatively greater effective target site doses at higher doses, resulting in a likely explanation for the nonlinear carcinogenic dose-response. Following initial exposure, high formaldehyde concentrations impair mucociliary clearance, stimulate cell proliferation, and increase the replication rate in respiratory epithelium (*89*). This, at least initially, increases the single-strand fraction of respiratory mucosal DNA, which is susceptible to covalent binding with formaldehyde. The latter data, however, do not indicate the concentration of formaldehyde at a target site relative to the concentration in air. Therefore, the panel recommends the use of airborne concentration for dose-response modeling at this time. The actual target dose is not known at this time but more information is being collected which bears on this issue (*254*). Alternative expressions for the target dose may be utilized.

1a., 1b.1, 1b.5, 1c. Low Dose Extrapolation. Mathematical risk estimation models are only mathematical constructs which can assist in evaluating dose-response relationships. Risk estimation models are no better than the data and the biological and mathematical assumptions on which they are based. Predictions of human risk derived from animal data must be considered in conjunction with human (epidemiological) data and qualitative biological data, such as the type of tumor produced in experimental animals, the mechanism by which tumors appear to be induced, interspecies comparisons, the actual dose delivered to the target tissues, and other factors.

At the present time there is general agreement that, because of the complexity of the carcinogenic process and the fact that we understand so little of the pathogenesis of cancer, there is uncertainty in the nature of the dose-response relationships for cancer production at low levels of exposure, specifically at those levels which do not produce observable effects in animal experiments or in epidemiological studies.

The use of data obtained at high doses in long term animal bioassays to predict carcinogenic risk at low dose is one of the most controversial issues in risk assessment methodology. This is also true in the case of formaldehyde, where the CIIT rat dose-response curve is highly nonlinear between the concentrations of 2 and 15 ppm. The observed experimental data in the CIIT inhalation study on rats can be fit reasonably well by using a sufficiently flexible family of models (e.g. Weibull, gamma-multihit, generalized multistage). The corresponding estimated models provide estimates of risk at any selected dose level. These estimates are those which are most consistent with the presumed family of dose-response models and their associated assumptions about background. If no explicit low-dose linear term is included in these models, these models assume no dosewise additivity with other carcinogens present in the environment or with background carcinogenic processes.

Upper and lower confidence limits on the risks being modeled may be computed to reflect the variability in the data under the presumed family of models. These confidence limits do not reflect the uncertainty in the choice of the family of models. Not all points in a confidence interval or all points below an upper confidence limit for the above presumed family of models are equally likely to be the true value of the quantity being bounded. These estimates and confidence limits are helpful as long as the underlying dose-response relationship is reasonably well described by the presumed family of models. The major difficulty is that, because of the complexity of carcinogenic processes and our limited understanding, there is usually considerable uncertainty about the shape of the dose-response relationship for doses near zero and hence the appropriateness of the low-dose behavior of the presumed family of models. The panel realizes that the very low-dose behavior of different families of models can be dramatically different.

The Risk Estimation Panel is aware of several possible reasons for the nonlinear carcinogenic dose-response observed with formaldehyde in the CIIT study. The Carcinogenicity/Histopathology/Genotoxicity Panel states: "Cytotoxicity might influence both initiation and promotion. If more cells of the target tissue replicate, there is greater availability of single-stranded DNA for adduct formation, decreased time for repair of DNA adducts, and a greater chance of fixation of mutagenic events.

Increased cell proliferation also contributes to tumor promotion. Thus, there is a greater likelihood of tumor development with the increased cell proliferation associated with cytotoxic exposures. These factors are likely to contribute to the nonlinearity of the dose-response, i.e., proportionately greater response at higher doses." The Structure Activity/Biochemistry/Metabolism Panel states: "Only certain specific sites on DNA might led to carcinogenesis; moreover, the rapid and nondiscriminate attack of formaldehyde on tissue components could involve membrane function, transport and repair processes, and it is known that mucociliary removal of formaldehyde is inhibited at high concentrations. In view of this complex network of reinforcing and competing reactions, it is not surprising that the carcinogenic response is not linear or that it does not parallel the degree of crosslinks. Although the cause is still uncertain, this apparent nonlinearity cannot be construed to indicate the existence of a threshold for exogenous formaldehyde carcinogenicity. Although nongenetic factors may play a role, more sensitive methods will be required to determine whether a linear relationship between dose and response exists at low exposure levels."

The Risk Estimation Panel could not reach a consensus on the way in which the uncertainty in choosing a family of nonlinear models should be incorporated into the risk assessment process.

Regardless of the model chosen, the panel is aware of several general arguments often made in support of low-dose linearity. Ehrenberg et al. (*255*) have pointed out that the kinetics of the various chemical processes involved in the uptake and metabolism of chemicals, and their reactions with target molecules, become first order at low concentrations, leading to low-dose linearity on the delivered dose scale. It has been suggested that when the action of a given carcinogen adds to those of other causes of cancer in a given target tissue, the incremental effect of small delivered doses of the given carcinogen is virtually linear regardless of the observed shape of the dose-response relationship at the tested doses (*256–259*). The rationale is that the carcinogen is augmenting some background component in causing a carcinogenic event. Formaldehyde shares with other chemical carcinogens the properties of genotoxicity and an ability to react directly with DNA (as concluded by the Structure Activity/Biochemistry/Metabolism and Carcinogenicity/Histopathology/Genotoxicity Panels). Further, the latter panel found that formaldehyde can transform, as well as mutate, various cultured cell lines and enhance the transformation of Syrian hamster embryo cells harboring adenovirus. Research at the CIIT has shown, additionally, that formaldehyde can initiate and promote the actions of other promoters and initiators in *in vitro* mammalian cultured cell transformation assays (*109,116*). These data suggest that formaldehyde can interact with several carcinogenic agents or processes.

The uncertainty over the shape of the dose-response relationship in the low dose region and the corresponding uncertainty over the appropriateness of the low-dose behavior for the family of models used to model the dose-response relationship in the experimental dose region has encouraged many members of the panel to suggest that a linear low dose nonthreshold extrapolation be used in risk assessment. A straight line connecting the risks at the endpoints of a low dose region provides an upper bound on low dose risks for dose-response relationships which curve upward in the low dose region (*260–263*). Low-dose linear extrapolation is not equivalent to fitting a straight line or a one-hit model to the experimental data. A highly nonlinear model is required, in the case of formaldehyde, to fit the experimental data. Linear extrapolation is only intended to be used at the low doses where adequate experimental information is not directly available due to the large numbers of animals required to measure small levels of risk. A nonlinear model which adequately fits the experimental data for the CIIT chronic rat inhalation bioassay could be used in conjunction with a low dose linear extrapolation procedure. The Risk Estimation Panel is in general agreement that a linear low-dose nonthreshold extrapolation provides an upper limit on cancer risk in rats exposed to formaldehyde by inhalation in the sense that the true risk in rats is not likely to be greater than this limit. The Risk Estimation Panel has not reached a consensus as to either the practical application of these upper limits for human exposures or the exact range of the low-dose region over which a linear extrapolation might be reasonably performed.

With regard to the possibility of a threshold dose for a tumor response, in the absence of any clear evidence at this time for a threshold, the Risk Estimation Panel believes that a threshold model for formaldehyde is not indicated.

It is important to note that the quantal dose-response models use only one biological endpoint, tumor incidence, at any selected point in time and only consider the dose-response relationship in terms of this endpoint. More information may be obtained by incorporating time-to-tumor onset information (*263,264*). The impact of the dose level on the length of time until a tumor occurs may be part of the risk characterization. It should be noted that dose includes the components of concentration of the agent and of the duration of exposure (*255*). The CIIT data show that the tumor rate is strongly dependent on formaldehyde concentration, but time-to-tumor onset may also be investigated. In addition, the length of time and the number of animals that were at risk in the CIIT study is complicated because animals were scheduled for interim sacrifices. Thus, the numbers of animals at risk need to be adjusted to take these sacrifices into account.

Conclusions. Available animal and human studies provide information to qualitatively establish various toxic effects of formaldehyde exposure, but quantitative assessment is not indicated at this time for biological effects other than carcinogenicity.

Although some epidemiological studies noted that there may be an association between formaldehyde

exposure and some forms of cancer, the data from these studies are not sufficient, at this time, for quantitative risk modeling.

The CIIT and NYU animal studies (*84*) indicate that cancer results in rodents from exposure to formaldehyde. Formaldehyde has also been shown to be genotoxic. The CIIT chronic inhalation bioassay in rats provides a set of data suitable for quantitative risk assessment. This data set, the use of a nonthreshold low-dose linear extrapolation, and the use of various plausible assumptions based on the available biological information regarding factors such as species to species extrapolation, metabolism and pharmacokinetics, provide an upper bound for low-dose risk estimates in the sense that the true risk in humans exposed to formaldehyde by inhalation is not likely to be greater than this limit. Nonlinear models are needed to fit the CIIT rat inhalation bioassay data over the experimental dose range, but estimates of risk from these models may vary at low doses. The panel could not reach a consensus on the way in which the uncertainty in choosing a family of nonlinear models should be incorporated into the risk assessment process.

Topic 2. Future Studies

Required are long-term follow-up on epidemiological studies along with measurements of formaldehyde dosage levels; improved measures of target dose; animal bioassays to study tumor rates resulting from short-term or intermittent formaldehyde exposures.

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Appendix I: Data Base of the Consensus Workshop on Formaldehyde

The literature comprising the data base, listed following this introduction, was made available, as reprints, as they were acquired, to the panel chairmen up to six months prior to the workshop. They were also available for all workshop participants at the meeting. The data base was organized by author as well as by a keyword index of important topics, and it was complemented by materials that the different participants brought with them and used as part of their participation in the panel. In some cases, studies in the data base were specifically cited as references in the individual panel reports, and no attempt has been made to remove these previously cited studies from the appendix. Hard copies of all the reports in this computerized data base have been retained by the NCTR Clearinghouse on Formaldehyde, as part of the agreement with the EPA.

Data Base for Formaldehyde Consensus Workshop

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